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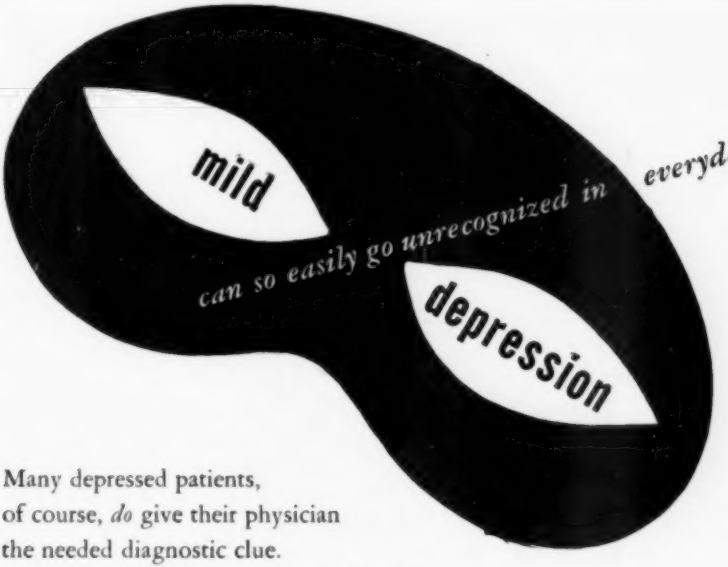

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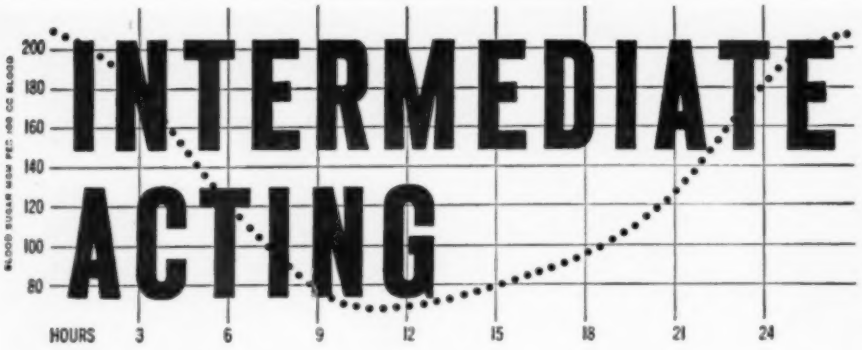

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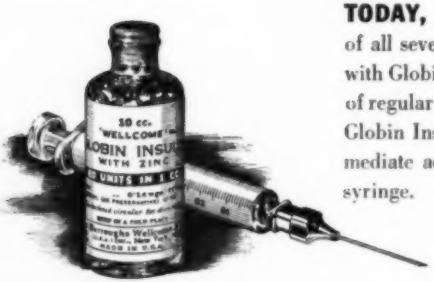

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1. Rohr, J.H., and Colwell, A.R.: Arch. Int. Med. 82:54, 1948.
2. ibid Proc. Am. Diabetes Assn. 8:37, 1948.

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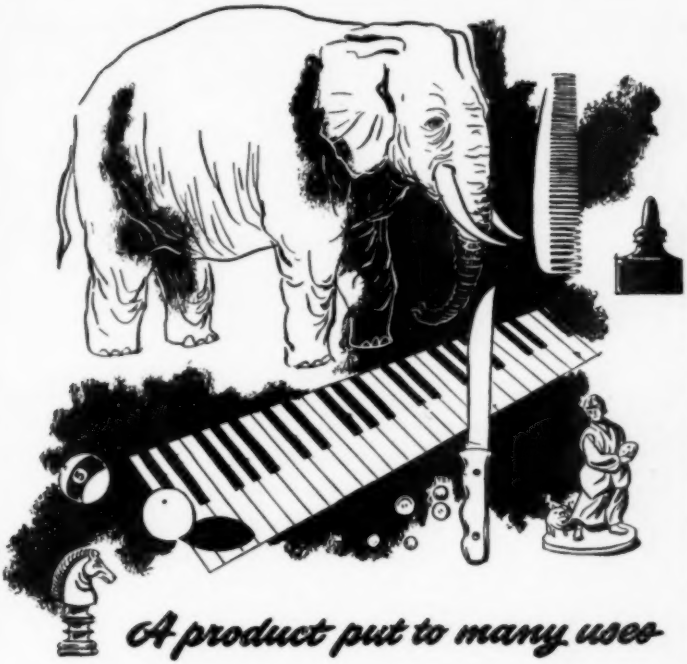

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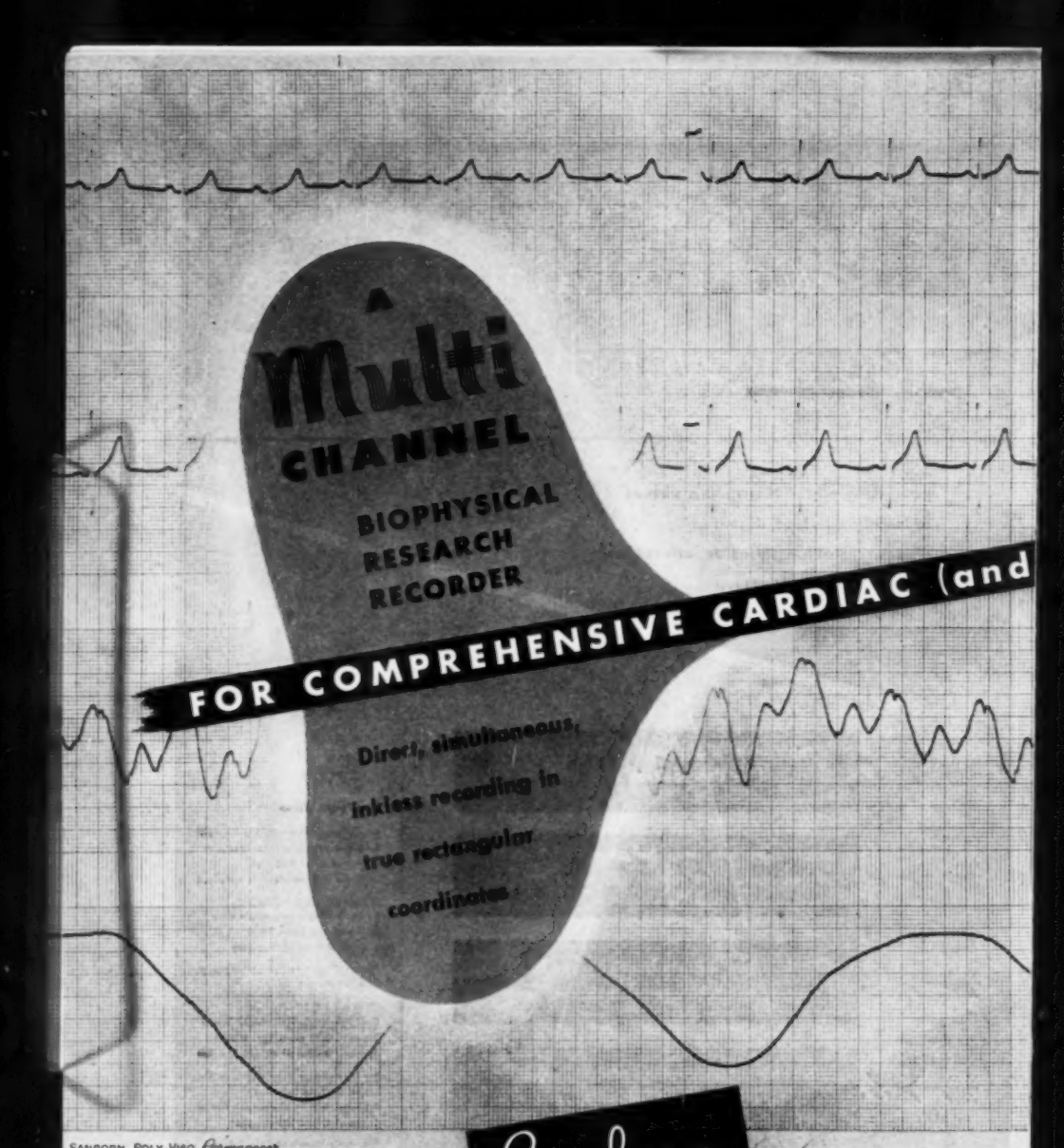

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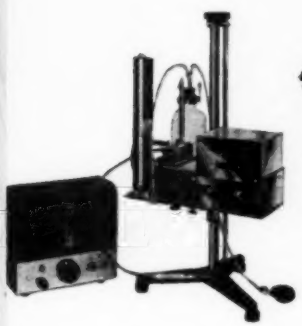

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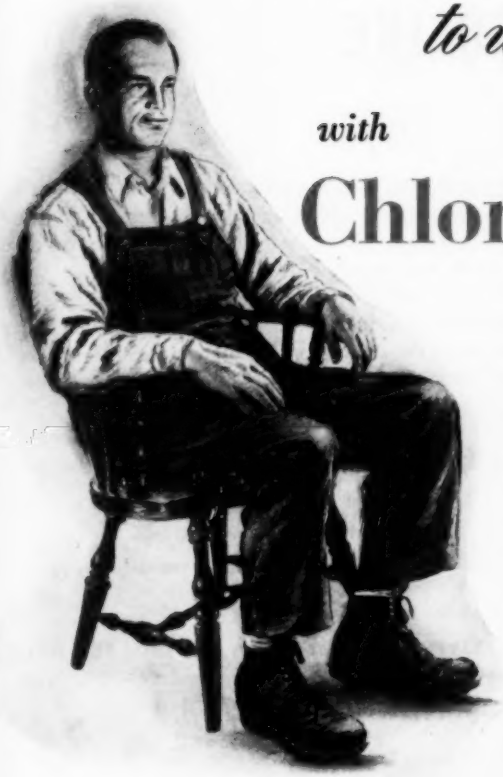

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1. Rawls, W. B.: New York Med. (no. 15) 3:19, 1947.

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ANNALS OF
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VOLUME 31 NOVEMBER, 1949 NUMBER 5

THE ETIOLOGY OF RHEUMATIC FEVER*

By HOMER F. SWIFT, M.D., *New York, N. Y.*

ALTHOUGH a causative rôle of streptococcal infections with respect to rheumatic fever is fairly widely accepted, the evidence for this opinion seems insufficient for the hypercritical. There are at least three attitudes concerning this question: (1) Acceptance of the thesis and a readiness to apply it practically to public health aspects of the problem; (2) Relative indifference to the information that has been laboriously collected and correlated; (3) Skepticism and reiteration of the statement that the cause of this disease is unknown, or claims that an unidentified virus is the offending agent. It is imprudent to belittle the rôle of a devil's advocate in any philosophical, political, or scientific discussion, for when he performs his task wisely, he will prevent proponents of a thesis from falling into errors, which may have serious and even fatal repercussions in the medical disciplines. It is important, nevertheless, not to allow his arguments to overwhelm the significance of careful observations and thus prevent their effective utilization. In current propaganda and appeals to the public for funds to support research in this disease, it is wise not to have assertions of our ignorance belittle the importance of well established data. Because these data may not appear simple in their relationships, there is danger that they may be ignored and their practical significance be neglected. The purpose of this lecture is to assemble various elements in the puzzle of the rheumatic fever problem and to arrange them in a satisfactory design, with the qualification that the nature of science is to grow and rearrange the elements forming its structure.

Probably the discovery of the action of salicylates in alleviating the toxic and painful manifestations of rheumatic fever materially hindered fundamental investigation of this disease. The symptomatic relief induced created a false sense of accomplishment; and not until several decades after

* Kober Lecture, delivered at Georgetown University Medical Center, Washington, D. C., March 28, 1949.

Delivered in part before the Thirtieth Annual Session of the American College of Physicians, New York, N. Y., April 1, 1949.

From the Hospital of The Rockefeller Institute for Medical Research, New York City.

this discovery had elapsed was it well demonstrated that the chronic heart disease, the real health menace of rheumatic fever, pursued its relentless course in spite of the relief of early symptoms afforded by salicylates.

The cost of rheumatic cardiac cripples far outweighs the expense in time, thought and money that have so far been applied to the prevention of the initiating disease. There are several convincing demonstrations that properly conducted prophylactic programs can be effective, but in so far as I am aware, few of the lessons in this field, learned just prior to or during the recent war, are being extensively applied or recommended in either military or civilian programs.

I am anticipating the thesis that a peculiar upper respiratory infection is important in the pathogenesis of this disease. Perusal of patients' histories almost two centuries old reveals descriptions of cases of acute articular rheumatism that followed closely in the wake of a severe sore throat. Probably the word "rheumatism" arose from the concept that a noxious humour "rheum" flowed from the inflamed throat to the joints; a concept not without merit today. Early in the last quarter of the 18th century, excellent clinicians reported that among some series of patients with acute articular rheumatism, at least 80 per cent had a preceding follicular tonsillitis within four days to four weeks of the onset of their rheumatism. During the succeeding 20 years there was much discussion concerning the significance of this sequential relationship; and at the end of the 19th century, Pribram,[1] in reviewing the literature on this subject, reported in different series of cases variations of from 1.7 to 80 per cent of recorded connection between the two diseases. Some clinicians also reported mild nasopharyngitis or otitis media as precursors of rheumatism.

Bacteriological studies did not resolve the differing opinions on this problem, for pneumococci, staphylococci, Pfeiffer's bacilli as well as streptococci were cultured from the sore throats, although the finding of streptococci outnumbered the others in frequency. Bacterially induced polyarthritis (somewhat resembling acute articular rheumatism) for example gonococcal or postdysenteric, confused the picture still more; and inability to distinguish hemolytic from nonhemolytic streptococci, the latter normal inhabitants of many human throats, left, at best, insecure ground for the proponents of a probable streptococcal causation of rheumatic polyarthritis.

The dilemma is well illustrated in the writings of Poynton and Paine,[2] who valiantly supported this thesis. Analysis of their bacteriological data indicates that in some cases they were dealing with *Streptococcus pyogenes* septicemia terminally complicating genuine rheumatic fever, and in others with subacute bacterial endocarditis superimposed on old rheumatic scarred valves. In their day, most observers regarded valvular endocarditis as being always induced by bacteria implanted on, or pressed into, the endothelial covering of the valves, a concept that has subsequently undergone considerable modification.

A forward step in streptococcal classification resulted from Schottmüller's blood agar plate technic for distinguishing hemolytic from nonhemolytic streptococci,[3] and the demonstration that the former comprised the more virulent strains. The frequent association of subacute bacterial endocarditis (endocarditis lenta) with chronic rheumatic valvular disease led many physicians to conclude that both conditions had as common causative agents the nonhemolytic streptococci which induced the finally fatal infection. This opinion was supported by the occasional post mortem recovery of viridans streptococci from the heart's blood of rheumatic subjects, for formerly bacteriologists little appreciated how rapidly, during the death agony or post mortem, green streptococci or enterococci may invade the blood stream from the mouth or intestines where they normally reside. Moreover, the temporary entrance into the blood of lowly virulent nonhemolytic streptococci following nose and throat operations, tooth extractions, instrumentation of the urethra or ureters, or manipulation of intensely inflamed pharyngeal tissues are phenomena, discovered in the past three decades, that explain the occasional recovery of green streptococci from the blood of rheumatic patients during life. It is, indeed, readily understandable how rheumatic fever-inducing properties were attributed to lowly virulent nonhemolytic streptococci, because the lesions they induce are usually nonpurulent, a characteristic of those of rheumatic fever; while in contrast, hemolytic streptococci are often pyogenic. Indeed, the impossibility of demonstrating pyogenic streptococci either in cultures of rheumatic exudates or proliferates, or microscopically in the visceral, articular, or subcutaneous lesions of rheumatic fever patient are features that could blind investigators to their potential pathogenic rôle in this disease. It appeared probable, moreover, that if the rheumatic lesions were invaded by streptococci, such lesions would more readily dispose of the easily phagocytable viridans varieties than of the more virulent pyogenic hemolytic strains. Indeed we formerly attributed to the viridans streptococci a possible etiologic rôle in rheumatic fever, an opinion that now seems incorrect; but it stimulated animal experimentation and the study of the host-parasite relationships which eventually seem to have added to knowledge concerning this disease. Before discussing these experiments, it is advisable to orient ourselves concerning modern streptococcal bacteriology.

In the early 1920's the classification of streptococci was based mainly upon three general procedures: (1) determining their action on blood; (2) testing their ability to attack certain chemical substances of known composition which were added to artificial culture media; and (3) ascertaining their capacity to survive under critical chemical and thermal environments.[4] While identification on such biochemical bases is sometimes definitive, notably with *Streptococcus mastitidis, Streptococcus equi,* the enterococci and *Streptococcus lactis,* many other streptococci have several common biochemical capacities but different pathogenic potentialities; hence the resulting

confusion could not be easily resolved. This apparent chaos in the world of streptococci has largely disappeared, thanks in considerable measure to the discoveries of Lancefield[5] and her collaborators in our laboratories combined with those of Griffith [6] in London.

Recognition of the existence of at least 12 serologically recognizable groups (table 1) in addition to the ungrouped viridans varieties favored correlation of etiological relationships among certain streptococcal groups

TABLE I

Serological Groups of Streptococci

Group	Common Name	Usual Habitat	Usual Pathogenicity
A	Human *Str. pyogenes*	Man	Many human diseases
B	*Str. agalactiae* (*Str. mastitidis*)	Cattle	Mastitis
C	*Str. equi* Animal *Str. pyogenes* Human C *Str. dysgalactiae*	Horse Many animals Man and animals Cattle	Strangles Many animal diseases Respiratory and other infections Mastitis
E	Group E	Normal milk	None
F	Group F (minute)	Man	Slight; respiratory tract
G	Group G (minute) Group G (large colony)	Man Man Dogs	Upper respiratory tract Many areas Genital and respiratory tracts
H	Group H	Man	Questionable; respiratory tract
K	Group K	Man	Questionable; respiratory tract
L	Group L	Dogs	Genital tract
M	Group M	Dogs	Respiratory tract
D	Enterococci: *Str. fecalis* *Str. liquefaciens* *Str. zymogenes* *Str. durans*	Intestinal contents Man, many animals and dairy products	Gastro-urinary tract, gastro-intestinal tract, abscesses, heart valves, wounds, contaminated food poisoning
N	*Str. lactis:* *Str. lactis* *Str. cremoris*	Milk Cream	None None

or sub-groups and certain diseases of man, domestic and wild animals, fowls and insects, respectively. To elaborate upon this interesting and important topic at this point [4] would lead us too far from the subject of this communication; but the demonstration that approximately 95 per cent of streptococcal infections in man are caused by members of group A has favored a rational direction of attention towards phenomena connected with microörganisms belonging to this group.

Somatic Antigenic Components

Groups are recognizable serologically because the strains within a group elaborate in common a group specific carbohydrate called C which gives a precipitin reaction in vitro when combined with its group specific antibody. Many groups are further divisible into serological types. The type specific components are sometimes polysaccharides, for example in group B, and sometimes, notably in group A, they are proteins which are designated type specific M substances.

The typing of group A streptococci stems primarily from the ability of a particular strain to induce in animals the ability to resist infection with that strain and also with other strains that elaborate a homologous type specific M protein. This resistance or type specific immunity may be actively induced by nonlethal infections, and also by parenteral injections of vaccines prepared from strains elaborating type specific M protein, but not from strains lacking this capacity. The serum of actively immunized animals

Table II

Somatic Antigens of Group A Streptococci

Somatic Antigens	Antibodies	Specificity
C carbohydrate	Anti C precipitins	Group specific
Nucleoproteins	Antinucleoproteins	Common to many cocci
T proteins	Anti T agglutinins	Some type specific; some common to several types
M proteins		Type specific
	Protective	in vivo
	Bacteriostatic	in vitro
	Anti M precipitins	in vitro*
	Anti M agglutinins	in vitro*

* With properly absorbed sera.

when injected in sufficient quantities into other animals protects them from infections with streptococci belonging to homologous types, but not from heterologous types.

Sera having this type specific protective capacity contain type specific antibodies. Of these, the most easily recognizable in vitro are anti M precipitins, which form precipitates after mixing suitable extracts of the streptococci in question with properly absorbed sera from highly immunized rabbits. Sera of men or animals infected with group A streptococci, or immunized with these bacteria, also contain agglutinins which may have type specific significance, provided accompanying non-type-specific agglutinins are suitably absorbed from the sera. This important proviso requires attention because many group A streptococci contain another somatic agglutinogen, called T, that sometimes bears a close type relationship to an accompanying M protein, and at other times does not. For example, types 4, 24, 26, 28, 30 and 44 elaborate T antigens so closely related that on the basis of agglutination tests with unabsorbed sera no single one of these types

can be identified from the other, although each type elaborates an M protein specific for that respective type. Furthermore, the antibodies against the T antigen bear no close relationship to protective antibodies or to type specific immunity, a relationship easily demonstrated with anti M precipitins.

Another substance closely associated with type specific immunity to group A streptococcal infections is the so-called bacteriostatic antibody, that renders virulent non-phagocytable streptococci liable to phagocytosis by leukocytes. In the direct bacteriostatic method complement, a thermolabile factor, and the leukocytes are contained in the blood of the individual being tested. If that blood contains the type specific bacteriostatic antibody, certain numbers of streptococci causing that patient's infection will be killed when mixed with the blood obtained shortly after venipuncture; if it does not, they will survive and grow on suitable media.[7] In the indirect method, complement, thermolabile factor and leukocytes are derived from the blood of a person presumably not previously infected with group A streptococci, and the bacteriostatic antibody in question is sought in the serum of the patient being considered. With this technic many sera obtained successively over long periods from the same patient and suitably preserved can be tested simultaneously, their antibody content measured quantitatively and its duration determined.[8] This test is quite type specific, and the bacteriostatic antibody detectable with it reflects a corresponding type specific resistance on the part of the patient who furnished the serum.

An interesting incidental observation has come from employing the blood of presumably normal adults to supply complement, thermolabile factor and leukocytes: these bloods, even without the addition of immune serum, may inhibit the growth of some strains of streptococci; and this phenomenon suggests that such bloods contain bacteriostatic antibodies stemming from previous streptococcal infections, which may have been either clinical or subclinical. This suggestion is further supported by observations that bacteriostatic antibodies rarely occur in the blood of quite young children, who probably have experienced few if any streptococcal infections. Furthermore a patient's serum obtained near the onset of a group A streptococcal infection practically never contains bacteriostatic antibodies specific for the streptococcal type that is inducing his latest infection; while most of these patients elaborate type specific antibodies against that type within a few weeks of infection, presumably due to type specific antigenic stimulation from his latest infection.

The bacteriostatic technic for studying antibody production by patients is the only in vitro test that gives results as strictly type specific as those furnished by passive protection of animals with immune sera, for both agglutination and precipitin tests with patients' sera often yield cross reactions with strains of other types. These non-type-specific reactions are partly attributable to the elaboration, by a patient infected with streptococci, of antibodies against several streptococcal somatic components or their metabolites, and partly to impure reagents. It is not yet possible to prepare streptococcal

extracts containing only M protein, for they usually contain residual antigenic substances that yield cross reactions with unabsorbed sera. In fact, suitable extracts prepared from group A hemolytic or viridans streptococci, pneumococci, or even staphylococci contain nucleoproteins which give cross complement fixation reactions with the sera of animals immunized with several varieties of streptococci, and with sera of patients suffering from subacute viridans streptococcal endocarditis, from acute group A streptococcal respiratory infections, or from pneumococcal pneumonia.[9] These results indicate that, in addition to the group or type specific components, the several members of the coccus family form somatic antigenic mosaics containing nucleoprotein-like substances with similar chemical configuration. Such phenomena point to the need for caution in interpreting the significance of both in vivo and in vitro tests performed with only partially purified streptococcal extracts.

Extracellular Antigenic Components

The serological reactions just discussed involve somatic antigens contained in streptococcal cells. Human subjects and animals while undergoing group A streptococcal infections or artificial immunizations, often form antibodies against extracellular products of streptococci. These extracellular antigens are elaborated into media nurturing these microörganisms and into the tissues of animals harboring them. Among the many extra-

Table III

Extracellular Antigens of Group A Streptococci

Extracellular Antigens	Antibodies	Relative Antibody‡ Production in Human Infections	
		No RF	*RF*
Streptolysin O	Antistreptolysin O	++	+++
Streptolysin S	Antistreptolysin S	++	+
Streptokinase (Fibrinolysin)	Antistreptokinase	++	+++
Hyaluronidase (Types 4 and 24) (Hyaluronidase precursor?)* all types	Antihyaluronidase	++±	++++
Proteinase	Antiproteinase	(+)?	(+±)?
Desoxyribonuclease (Dornase)†	Anti-DORNase†	+	++
Ribonuclease	Antiribonuclease	?	?
Erythrogenic toxin	Antitoxin	?	?

* The existence of a precursor is assumed because of the frequent stimulation of streptococcal antihyaluronidase following most group A streptococcal infections.

† The abbreviation DORN is derived from DesOxyRiboseNuclease (Tillett et al.).

‡ The designation "relative" refers to statistical analysis of groups of patients and not to one individual.

cellular antigens, those longest studied are erythrogenic toxins, streptolysin O, and fibrinolysin, more accurately designated streptokinase; others have more recently attracted attention.

It is now generally accepted that scarlet fever is caused by group A streptococci that elaborate a rash-inducing toxin against which the patient possesses no effective antitoxic immunity when infected. This toxin cir-

culates in his blood during the acute phase of scarlet fever, and stimulates the formation of antitoxins that accompany and probably effect recovery. Many people apparently develop these toxin-neutralizing antibodies without suffering from scarlet fever, but probably from infections with streptococcal strains that elaborate insufficient erythrogenic toxin to induce a rash but still enough to induce the production of antitoxin. Once having developed this antitoxic immunity, most persons retain it the rest of their lives; hence they may subsequently undergo severe infections with erythrogenic toxin-producing streptococci without developing a rash. The erythrogenic toxin is probably not involved directly in the pathogenesis of rheumatic fever; but scarlet fever, being a group A streptococcal disease, is consequently a frequent precursor of rheumatic fever; hence the old designation "scarlatinal rheumatism" has nosological significance mainly because it supports the thesis that group A streptococcal infections induce rheumatic fever.

Streptolysin O is an extracellular hemolysin elaborated by most strains of group A streptococci and a few strains of groups C and G. An antibody, designated antistreptolysin O, which neutralizes its hemolytic properties in vitro, occurs in the sera of animals following injections with large amounts of cell-free streptolysin, or after suitable streptococcal infections.[10] It also often appears and usually increases progressively in strength in the sera of patients recovering from group A streptococcal infections[11] provided the infecting strains elaborate this lysin. When they do not, a patient elaborates no antistreptolysin O in his serum. Some patients, however, even though infected with hemolysin-O-producing strains fail to develop antistreptolysin O. A rising titer of this antibody after an infection is strong presumptive proof of its group A streptococcal etiology. Such antibody production, frequently observed in rheumatic fever patients, has furnished very convincing evidence that group A streptococcal infections are precursors of their rheumatic attacks. That this test is not specific with respect to rheumatic fever, but only to the precursory streptococcal disease, should be emphasized, and also that a negative test does not eliminate the possibility of such a streptococcal precursory infection.

Streptokinase, a component of streptococcal fibrinolysin,[12] is also found in media supporting growth of many streptococci belonging to group A, to some of groups C and G, and rarely to group B. It activates a precursor, plasminogen, present in most human sera, to form plasmin, an active fibrinolytic agent.[13] Patients infected with streptokinase-producing streptococci elaborate an antibody called antistreptokinase (formerly antifibrinolysin) which is quantitatively measurable in test tubes.[14] A *rising* titer of this antibody in the sera of rheumatic patients has significance comparable with that of antistreptolysin O: viz., it indicates a recent group A streptococcal infection; but a continually high titer may occur and be the result of infections many months previously.

Other antigenic and/or enzymatic substances elaborated into their nu-

tritional environment by group A streptococci and their respective antibodies require consideration.

Hyaluronic acid, hyaluronidase and antihyaluronidase have recently attracted considerable attention with respect to a possible pathogenic relationship in rheumatic fever. This acid, a highly viscid polysaccharide, makes up the capsules formed by many streptococci belonging to groups A and C.[15] Its presence bears close relationship to the virulence of "animal" group C streptococci,[16] but it has only slight significance in the virulence of group A strains.[17, 18] Hyaluronic acid is widespread in the bodies of vertebrates, notably in the umbilical cord, vitreous humor, synovial fluid, and in the interfibrillar cement substance of collagen.[15] Enzymes that split it are designated hyaluronidases, and several have been described from different sources: leech heads, mammalian testicular extracts, groups A and C streptococci, pneumococci, staphylococci and clostridia. While the common action of the enzymes from these different sources is to split any hyaluronic acid into less complex and viscid products, each hyaluronidase appears to be antigenically specific according to its respective origin; e.g., antihyaluronidase in the serum of persons infected with group A streptococci does not react with hyaluronidase from other bacteria. Three technics for demonstrating hyaluronidase have been employed: mucin clot solution; turbidity reduction; and as a spreading factor (Duran-Reynals[19]). Antibodies against hyaluronidases are measured by their ability to prevent these actions. With the mucin clot prevention technic and a substrate from umbilical cords, hyaluronidase production has been demonstrable only with type 4 and type 22 group A streptococci[20]; but Pike,[21, 22] employing the turbidity reduction technic with hyaluronic acid from streptococcal capsules, found hyaluronidase production by over half of his noncapsulated group A strains and even by some capsulated strains. The possibility that most group A strains form this enzyme, usually as a precursor must be entertained, for although it is difficult of demonstration in vitro, the fact that most patients infected with group A streptococci elaborate streptococcal antihyaluronidase indicates its widespread occurrence in these microörganisms. The degree of this antibody response, moreover, suggests that hyaluronidase is a very strong antigen, possibly the strongest of the extracellular antigens.

New born babies have practically the same streptococcal antihyaluronidase content in their sera as is present in that of their mothers; but this disappears within six months. Beginning in the three to five year age period, this antibody begins to appear with a slowly increasing frequency, until the age group of 20 years. The relative frequency curve then remains constant until the 60 year age group, when it falls slightly.[23, 24] This phenomenon, and the demonstration of antibodies against erythrogenic toxin slowly increasing with age, reflect roughly the occurrence of group A streptococcal infections in a considerable portion of the population.

The other three extracellular enzymes, proteinase,[25] desoxyribonuclease and ribonuclease,[26] have been much less studied with respect to different human infections; but it has been shown that antibodies are formed against the latter two by patients suffering from group A streptococcal infections both with and without subsequent rheumatic fever [26]; and by animals against the former.[27] These enzymes are probably relatively weaker antigens than hyaluronidase, streptolysin O and streptokinase. McCarty has pointed out that all of these streptococcal extracellular antigenic enzymes have functions comparable to the digestive enzymes found in the gastrointestinal tracts of vertebrates; and, in that they break down more complex molecules into simpler ones, they probably make available to the bacteria nutriment occurring in the media in which the microörganisms grow.

Streptolysin S, discovered by Todd [28] is apparently the most toxic in vitro of any of the known extracellular streptococcal antigens. Bernheimer [29] has recently defined quite minutely the cultural conditions under which it is most readily produced; hence it should be possible to investigate more readily than formerly the disease conditions and immunological states under which antistreptolysin S formation occurs. Studies already made on this subject are mentioned later.

The foregoing brief review of the somatic and extracellular antigens of group A streptococci and of their respective antibodies is requisite to a description of how these data have been applied in supporting the theory that members of this streptococcal group play an important rôle in the etiology of rheumatic fever.

Sequential Relationship Between Group A Streptococcal Infections and Rheumatic Fever

About two decades ago, Coburn [30] in this country and Sheldon [31] and Schlesinger [32] in England almost simultaneously redirected medical attention toward the probable rôle of streptococcal respiratory infections as precursors of rheumatic fever, both in first attacks and in recurrences. The studies of Griffith,[33, 34] and his collaborators in England, of streptococcal epidemics in barracks, boy's schools and in fever hospitals indicated that single epidemics were usually due to one type of streptococcus, and that different types were active in successive school terms. With Lancefield's technics for identifying streptococcal groups it has been demonstrated that all of the respiratory infections that preceded attacks of rheumatic fever are caused by group A streptococci. This unique sequential relationship has been firmly established by many observers, particularly during the recent war in training areas where various respiratory infections were rife, and where cases of streptococcal nasopharyngitis, tonsillitis, and scarlet fever occurred by the thousands. Furthermore, bacteriological technics and good clinical observations have established quite definitely that respiratory infections due to microörganisms other than group A streptococci are not precursors of rheumatic fever.

Carefully gathered data moreover have demonstrated that the precursory streptococcal infection may be so mild as to escape clinical detection. For example, Kuttner and Krumwiede [35] showed that during epidemics in a closed institution, streptococci appeared for a few days in the nasopharynges of some children, who then sometimes had slight leukocytosis, and subsequently developed in their sera increasing titers of antistreptolysin O. Others have confirmed this observation under epidemic conditions. Thus was explained the old observation that rheumatic fever occurs at times without an obvious nasopharyngitis as a forerunner: it may be too mild for accurate clinical detection.

Reactions in Patients' Sera with Extracellular Streptococcal Antigens

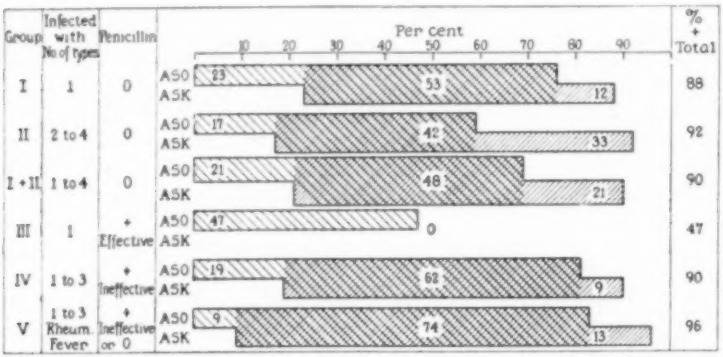
The streptococci inducing the precursory infection, moreover, disappear from the nose and throat before the onset of the rheumatism in a quarter to a third of the patients; hence other evidence of the precursory streptococcal activity is requisite; and the need has been supplied mostly by study of antibodies against the extracellular antigens of group A streptococci. Among these the antistreptolysin O test, devised by Todd,[10] has been most extensively employed; and with it between 80 and 90 per cent of rheumatic fever patients have been shown to develop abnormal amounts of antistreptolysin O in their sera. This is also true of most patients infected with group A streptococci; hence, this reaction is not diagnostic of rheumatic fever, but of group A streptococcal infections. That such infections may occur without inducing antistreptolysin O formation has already been noted; hence this test has only relative, not absolute value.

The application of technic for detecting antifibrinolysin,[12] and more recently for titering antistreptokinase quantitatively,[14] has still further confirmed the nature of the precursory respiratory infection, for sometimes there is an increase in antistreptokinase but no rise in antistreptolysin O, and vice versa. Several observers have reported a relatively higher content of these two antibodies in rheumatic than in non-rheumatic subjects, without having information concerning the antigenic composition of the streptococci infecting their patients; hence it was not known definitely whether the relatively greater antibody formation by the rheumatic group was due to differences in the parasites' activities or in the hosts' responses.

This question is apparently answered by the observations of Anderson, Kunkel, and McCarty [36] in a study of an epidemic in patients infected with strains of one or more of three different types of group A streptococci; so the antigenic stimulus was probably similar. Although, as in all such studies, there was marked variation among individuals, the group which had rheumatic sequelae developed distinctly more antistreptolysin O and antistreptokinase than did those who remained free of rheumatism. Other noteworthy observations were recorded: (1) those patients effectively treated

early with penicillin, who did not suffer rheumatic fever sequelae elaborated the smallest average amounts of these two antibodies, in fact, no detectable antistreptokinase; (2) in spite of low titers of these antibodies in this non-rheumatic group, the gamma globulin in their sera was significantly increased, an indication that other antibodies were probably formed; and (3) the average amounts of gamma globulin and antistreptolysin O were higher in the rheumatic fever group at the onset of their precursory streptococcal infections than in the non-rheumatic group. Hypothetically, this suggests that residual influences of previous group A streptococcal infections were more prominent or more durable in the rheumatic group than in the non-rheumatic, and that these residual influences may have "attuned" their tissues in the direction of a peculiar response to their latest streptococcal infection.

Antistreptolysin O and antistreptokinase production
by different patients infected with same types of Group A streptococci



Anderson, Kunkel, and McCarty

CHART 1.

Finally, these authors' observations, summarized in chart 1 indicate the advantage of applying more than one serological test when searching for antistreptococcal antibodies; and the negative findings emphasize the hazard of denying the existence of a streptococcal infection in a patient because a particular antibody cannot be found in his serum.

The relatively stronger concentrations of antihyaluronidase recorded by Friou and Wenner,[37] Quinn,[38] and Harris et al.,[39] have suggested that the hyaluronidase of group A streptococci might be playing a special rôle in the production of lesions of collagen of which hyaluronic acid forms a considerable portion. That such a mechanism is possible cannot be categorically denied; but if it is an important factor in the induction of rheumatic lesions, it would seem that the microörganisms producing the most hyaluronidase would be the most liable to induce rheumatic fever. This, however, is con-

trary to experience: although it has been demonstrated that among group A streptococci only types 4 and 22 produce hyaluronidase in amounts sufficient to be easily detected in vitro, nevertheless, in at least two epidemics caused by type 4 streptococci in rheumatic subjects, no rheumatic recurrences were induced, while rheumatic fever frequently follows infections with streptococci that produce relatively little hyaluronidase. Furthermore, group C streptococci, quite frequent producers of considerable amounts of hyaluronidase, have likewise not been observed to induce rheumatic fever; and pneumococci, staphylococci and clostridia, also potent producers of this enzyme, are conspicuously negative as inducers of rheumatic fever.

The report by Guerra [40] that hyaluronidase (probably in testicular extracts) acted as a spreading agent (Duran-Reynals [19]) more powerfully in rheumatic fever subjects than in non-rheumatics, and that this spreading action is inhibited in guinea pigs by salicylates, has also excited renewed interest in the possible hyaluronidase-antihyaluronidase question with respect to rheumatic fever. Harris and Friedman [41] employing relatively weaker concentrations of streptococcal hyaluronidase were unable to demonstrate any unusual susceptibility to this spreading factor in rheumatic fever subjects compared with non-rheumatics. They suggest that the differences in their results from Guerra's were due to the strong irritating effects of the extracts used by the latter, and that these nonspecific effects might easily lead to misinterpretation of the results he observed.

Until more light is thrown on the whole hyaluronidase subject, it seems well to assume that the relatively more marked antihyaluronidase formation by rheumatic fever patients, compared with that of patients with simple streptococcal infections, is a concomitant rather that a causal phenomenon with respect to rheumatic fever.

The question of antistreptolysin S production by rheumatic fever patients has received relatively little attention, probably because of technical difficulties in producing this antigen for in vitro studies. Todd, Coburn and Hill [42] reported that antistreptolysin S was more abundant in the sera of patients suffering from simple group A streptococcal infections than in that of patients with rheumatic sequelae, even though the latter contained more than was found in normal persons' sera. With better methods for preparing streptolysin S, reported by Bernheimer,[29] investigations of the relationship of this lysin to various manifestations of streptococcal infections will probably be resumed.

The occurrence in a patient's serum of antibodies against the extracellular components of group A streptococci merely indicates a previous infection with some strain belonging to this group, but has no significance with respect to any particular strain or type. Furthermore, the finding of abnormal concentrations in a single serum is not definitely indicative of a recent streptococcal infection, because fairly high titers of antistreptolysin O, antistreptokinase, or streptococcal antihyaluronidase may persist in a patient's serum for many months, possibly years, after a streptococcal infection. If

the titer is doubled or tripled in two or more sera successively obtained within a few weeks after an infection, however, a group A streptococcal causation of that infection is indicated.

Reactions in Patients' Sera with Type Specific Group A Streptococcal Antigens

Theoretically the development of antibodies against the somatic component M of group A streptococci should furnish fairly conclusive proof of infection of a patient by a strain belonging to the particular type from which M was derived. This question has been much less studied in patients than has the production of antibodies against the extracellular antigens; but for a period of four or five years there was carried out in our laboratories and clinic a comparative study of the development, by streptococci-infected patients, of antibodies against the type specific M component of the streptococci with which the respective patients were infected.[42] Some of the results are shown in table 4.

Table IV

Comparative Formation of Antibodies Against Group A Streptococcal Extracellular and Somatic Antigens, by the Same Group of Patients

Nature of Group A Streptococcal Infection	Uncomplicated	Complicated	With Rheumatic Fever Sequelae*	Total
Antibodies against extracellular antigens:				
Antistreptolysin O increase	69.7%	75.0%	85.3%	77.1%
Average beginning of rise	2.4 wks.	2.3 wks.	2.0 wks.	2.4 wks.
Antifibrinolysin increase	62.9%	80.0%	80.9%	73.0%
Average beginning of rise	3.1 wks.	2.5 wks.	2.3 wks.	2.6 wks.
Antibodies against somatic antigens:				
Bacteriostatic antibody increase	66.7%	68.8%	87.9%	75.6%
Average beginning of rise	4.2 wks.	3.9 wks.	6.1 wks.	5.1 wks.
Range	2–10 wks.	2–8 wks.	1–13 wks.	
Precipitin reactions with M extracts				
(a) Homologous type	45.5%	56.2%	85.3%	63.9%
(b) Heterologous type	33.3%	43.8%	61.8%	46.9%
Average beginning of rise	3.6 wks.	2.6 wks.	6.0 wks.	4.8 wks.
Range	1–8 wks.	1–5 wks.	1–23 wks.	

* 12% of rheumatic patients also had purulent complications (see reference 43).

This table summarizes the relative development at weekly intervals of antibodies against two extracellular antigens and two somatic antigens by a fairly large group of patients, who were divided into three subgroups: (a) those without complications or sequelae; (b) those with purulent complications; (c) those with rheumatic fever sequelae (but four of the latter also had purulent complications). It was not possible to measure an antifibrinolysin increase in some of the patients because of high concentrations of this antibody in their sera at the onset of their latest streptococcal infec-

tions, and the quantitative antistreptokinase test was not yet available; but a study of the comparative development of the other three antibodies was possible. The rheumatic fever group developed relatively average higher antibodies than did the non-rheumatic group when tested with these four different technics. Although the average measurable antibodies against the extracellular antigens appeared at practically the same time following infection in all groups of patients, there was an average delay of approximately two to three weeks in the appearance of antibodies against the somatic antigens among the rheumatic fever group as compared with the non-rheumatic; this is illustrated in the bacteriostatic and anti M precipitin tests, and confirms earlier less extensive studies.[44, 45] The possible significance of this delay in the pathogenesis of rheumatic fever is not as yet evident.

Chart 2, summarizing graphically the antibody production by a comparable series of our patients indicates that the more tests that are applied to the same lot of sera, the more convincing is the evidence of a previous recent

Distribution of 4 different antibodies
in 83 patients infected with Group A streptococci

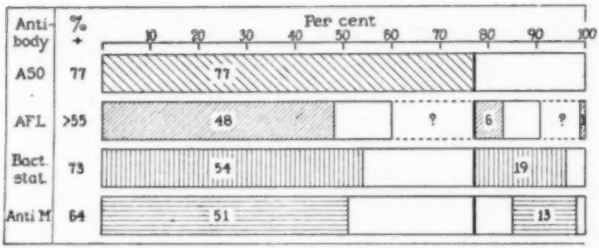


CHART 2.

streptococcal infection. Among patients undergoing 83 different group A infections, whose sera were repeatedly tested for antistreptolysin O, antifibrinolysin, bacteriostatic and anti M precipitin reactions, it was found that the first appeared in practically three-fourths of the cases; but among the patients' sera containing no antistreptolysin O, there was nevertheless a demonstrable formation of antifibrinolysin, bacteriostatic antibodies, or anti M precipitins; hence application of four tests indicates there was antibody formation against one or more streptococcal antigenic components in all instances.

A detailed analysis of this entire series of patients in whom it was possible to initiate the investigations very near the time of onset of their streptococcal infections and to continue them through the period when rheumatic sequelae were apt to occur, and in the event of the appearance of these sequelae for several months and sometimes for two or three years, showed the following: at the onset of an infection with a given type of group A streptococci, a patient's serum contained no bacteriostatic antibodies against that type, al-

though it often contained abnormal amounts of antistreptolysin O or antifibrinolysin, and sometimes of bacteriostatic antibodies against streptococci belonging to types heterologous to that recently infecting a patient. This indicated that streptococcal infections had existed in that respective patient prior to the most recent infection. The type specific bacteriostatic antibodies usually appeared later in the course of infection or with recovery, and at times persisted for months or years, though occasionally they were demonstrable for only a few months. They were probably an index of type specific immunity. Bacteriostatic antibodies against heterologous types found very early in an infection probably indicate previous infections with streptococci belonging to these respective types.

Multiple Group A Streptococcal Infections in One Person

A reorientation of our attitude towards human streptococcal infections has been brought about by the demonstration that most of them are caused by members of group A, and that this group comprises many immunologically recognizable types, of which about 40 have been identified with serological technics. Infection with one type leads fairly quickly to a specific immune resistance to that type, which, we may infer from data furnished by bacteriostatic tests, may persist for long periods. This inference is supported by experiments with monkeys that were rendered type specifically resistant to the homologous type of streptococci with which they were inoculated intranasally, but not to heterologous types.[46] In fact, type specific immunity in man does not insure resistance to other types, for there are numerous reports of superinfections of patients with streptococci heterologous in type from the original infecting strain. These superinfections frequently bring about complications, so that a patient may be simultaneously suffering from two different group A streptococcal infections. The possibility of cross- or superinfection indicates that, ideally, quarantine of patients should be based on the type that is infecting them,[47] an ideal rarely attained. Indeed, the rapidity with which streptococci can be made to disappear from the nasopharynx of a patient by intensive penicillin therapy, and the resistance to infection or to reinfection of persons receiving either sulfonamides or penicillin, make it easy to prevent the spread of streptococcal infections in families, schools, or other institutions (Massell et al.[48]).

For our present purposes, the phenomenon to be emphasized is the possibility, even probability, that one person may suffer several group A streptococcal infections during his life. This is indicated in many people by the following: a history of several different diseases usually caused by group A streptococci; the existence of immunity to streptococcal erythrogenic toxin, an immunity that increases roughly proportionally to age; the presence in many persons' blood of streptococcal antihyaluronidase, antistreptolysin O or antistreptokinase; the presence of bacteriostatic antibodies to several streptococcal types in the sera of many youths and young adults; and finally by the

demonstration that in one person suffering from repeated respiratory streptococcal infections, each attack has been induced by a group A streptococcus different in type from those shown to have caused previous attacks. This leads directly to the concept that in many people suffering from successive streptococcal infections, each infection is probably induced by group A streptococci different in type from those that caused prior infections in that person.

The varieties of nosologically definable diseases induced in human beings by group A streptococci are probably more numerous than is the case with any other microörganism. None of them, e.g., erysipelas or scarlet fever, is caused exclusively by a single serological type of streptococcus. The characteristic rash of scarlet fever is a peculiar response to an erythrogenic toxin elaborated by strains belonging to several types. Surgical or obstetrical streptococcal infections owe their peculiarity in part to the body areas invaded by the microörganisms, and in part to their virulence. In a streptococcal epidemic due to a single strain, such as occurs in milk-borne infections, and in families, institutions and barracks, many different clinical manifestations are observed; and this suggests that variations in the tissues of different persons are factors which help to condition the clinical pictures.

Powers and Boisvert [49] have outlined the changing types of response to streptococcal infections of the respiratory tract encountered at various age periods. In the very young, the symptoms are least clear cut; the nasopharyngitis is diffuse, of several weeks' duration, and prone to spread to the accessory sinuses and middle ears. The picture may be so noncharacteristic that its etiology can only be determined bacteriologically. Not uncommon is eczematoid dermatitis or vaginitis due to the same streptococci that are inducing upper respiratory infection. In school children, the nasopharyngeal response is somewhat more circumscribed and intense, the general symptomatology more stormy, the duration of a single infection shorter than in the very young. At the end of the first and in the second decade, especially after puberty, the course is usually still more acute, the fever higher, the duration shorter, the nasopharyngeal response more focalized and intense. Such turbulent and relatively brief acute courses exemplified by an attack of tonsillitis, are common in the third and fourth decades of life; and after 40, streptococcal respiratory infections are relatively much rarer than in the earlier age periods, which suggests that with advancing age a fairly effective immunity has developed.

Because these trends of streptococcal diseases towards localization resemble comparable phenomena seen in tuberculosis, Powers has designated the whole group of streptococcal diseases, "streptococcosis." It seems to me that because of the multiplicity of their clinical manifestations they may be more usefully compared with those of syphilis. This disease is currently so modified by antibiotics and other drugs that its normal evolution is difficult to observe.

In untreated or poorly treated syphilitic patients, the first response at the site of inoculation is a hard chancre, which is followed within a few weeks by

"spirochetemia." Then with intervening symptom-free periods, there occur successively the following manifestations: (1) widespread adenopathy and a diffusely generalized roseola involving most of the skin and visible mucous membranes; (2) finely papular syphilides, somewhat indurated, which tend to be grouped and to involve relatively less of the total integument than did the roseola; (3) larger syphilides more definitely grouped, fewer and of somewhat longer duration than those occurring previously; (4) comparatively late relapsing syphilides that are still larger grouped nodules, but often few in number. About the middle of the third year the lesions are large nodules or gummata, few in number, which may involve any tissue or any viscus. This changing character of the syphilides is attributable to a progressive retuning ("umstimmung") in the responses of the tissues in a body that is continually harboring *Treponema pallidum*. It is usually so well patterned that an experienced syphilologist can approximate fairly accurately the duration of a patient's syphilis from the character of his syphilides. Similar, but fewer clinical manifestations attributable to a somewhat comparable retuning of the tissues towards tubercle bacilli or tuberculin are seen in tuberculosis. Noteworthy is the granulomatous character of the lesions occurring in the tissues of a subject with such subacute or chronic infections.

The changing picture of streptococcal infections observed successively in infants, toddlers, school children, youths, and adults might well be conditioned by a comparable retuning of the patients' bodies to group A streptococci as the patients undergo repeated streptococcal infections, a retuning which results in a progressively increasing ability to focalize or limit the infections. While in the untreated syphilitic, the several relapses are all responses to infection with the one strain of spirochetes with which he was originally infected, this, as previously noted, is not true in one person with successive group A streptococcal infections, for many different serological types may, and probably do, infect one person; hence each infection constitutes a new disease in a body retuned, as a result of previous infections, to respond somewhat differently to his latest infection than to his former ones. After reaching the tertiary stage in syphilis the relapses are practically always gummatous; likewise, after a certain number of streptococcal infections the localized clinical responses tend to resemble one another even though the infecting strains belong to different serological types. In spite of their differences with respect to their M antigenicity, group A streptococci nevertheless have, in common, many other antigenic components which may stimulate the patients' tissues to a progressive retuning.

Experimental Streptococcal Infections

A valid criticism of the thesis that group A streptococci play a unique rôle in the etiology of rheumatic fever stems from a failure of investigators consistently to induce in lower animals, infected with these streptococci, lesions closely resembling those of human rheumatic fever. For many years

this has been one of the objectives of experiments in our laboratories; and while there were many failures in attaining the primary objective, still much information was obtained which, with simultaneous studies of streptococcal infections in rheumatic patients, has apparently advanced our conception as to how streptococci may act to induce this disease. The pertinent data deriving from those investigations follow.

The earlier researches were carried out with rabbits infected intracutaneously with viridans streptococci. By employing suitable strains, it was shown that after the primary inflammatory response had subsided there often appeared, at the sites of the original inoculations, secondary reactions lasting for one to five days.[50] These reactions resembled somewhat those described by Koch in guinea pigs infected with tubercle bacilli, and in many respects differed from the Arthus phenomenon in rabbits injected with foreign serum.[51] This state of bacterial hyperreactivity could be distinctly increased and prolonged by repeated minute focal inocula of the streptococci. Indeed, it seemed to derive, to a considerable degree, from inflammatory foci, for when comparable doses of the same lowly virulent streptococci were injected intravenously into rabbits the focal responses to subsequent intracutaneous inoculation were less marked than in normal controls; in other words a state of immune hyporeactivity had been induced. It was next shown that by injecting lowly virulent strains of hemolytic streptococci, or heat-killed cultures, the state of hyperreactivity was induced by intracutaneous inoculation and a state of immune hyporeactivity by intravenous injections.[52] It was then found that although rabbits immunized intravenously with a strain of viridans streptococci developed a state of immune hyporeactivity to intracutaneous challenge with that strain, their response to a simultaneous challenge with a group A or a group C strain was that of hyperreactivity.[53, 54] Also noteworthy was the observation that two or three months after stopping the intravenous immunization, there developed a state of hyperreactivity to challenge with the immunizing strain.[54] Subsequently, when the significance of successive human infections with several different serological types of group A streptococci was appreciated, it was shown that prolonged intravenous immunization of rabbits with one type of group A streptococci or repeated intracutaneous infections with one fairly virulent type, usually induced the animals' tissues to respond subsequently to suitably sized intracutaneous inocula as follows: immune hyporeactivity to challenge with homologous type strains; and frequently, though not always, the same animals showed cutaneous hyperreactivity to inoculation with heterologous type strains.[55]

Rheumatic Fever-Like Carditis Following Successive Infections with Different Types of Group A Streptococci

The probable import of one person having several streptococcal upper respiratory tract infections each with a different type of group A streptococci was at that time becoming increasingly insistent, for it seemed that with each

successive infection the patient's tissues were probably becoming retuned in a manner comparable to that observed in rabbits. It was, therefore, decided to test the effect of several successive inoculations of rabbits, each inoculation with a group A streptococcus of a type different from that which the rabbit had previously received. As it was obviously impossible to induce repeated infections in rabbits' throats, or to observe them satisfactorily if they were so induced, it was planned to test the effect of using the animals' skin as the organ for successive inoculations, and to employ varying intervals, each of several months' duration, between inoculations. Occasionally the same streptococcal type was employed twice. The results of these experiments, carried out by Dr. George E. Murphy and myself over a period of two and a half years, have been recently recorded.[58]

Briefly summarized, the results were as follows: After sustaining several focal cutaneous infections, some rabbits sickened, but many of these recovered; a portion were sacrificed within 10 to 14 days following the last infection. In a few, however, a severe fatal illness developed after the last intracutaneous infection. These fell into two subgroups: in about half dying between six and 14 days following the last infection, streptococcal bacteremia was demonstrated at autopsy; in the other half, however, streptococci could not be cultured from the blood either before death or at autopsy. In the hearts of successively infected rabbits that sickened and succumbed, and of those sacrificed while sick, there occurred microscopically demonstrable lesions closely resembling those encountered in the hearts of patients dying with rheumatic fever. Focal collagen and intercellular ground substance alterations have occurred in vascular adventitia, valves, chordae tendineae, mural endocardium, epicardium and in myocardial interstitium unrelated to arteries or veins. Many swollen collagen fibers stained, either entirely or in patchy fashion, like fibrin with connective tissue technics. Interspersed in fields of swollen collagen and altered ground substance, there occurred nodular collections of large, irregularly shaped cells, often with abundant, finely granular, basophilic, indistinctly outlined cytoplasm. The variously shaped vesicular nuclei, single or multiple, had sharply defined membranes. Numerous cells with two to 12 centrally placed nuclei were seen in some hearts in mitral and aortic sulci and valve rings and in the endocardium. The submiliary granulomata found in these rabbit hearts closely resemble the coronal, reticular and mosaic types of Aschoff bodies. Mitral and aortic interstitial valvulitis was commonly found; and marked proliferation of mitral and aortic sulcus and valvular endocardial and subendocardial cells often formed palisades containing numerous multinucleated giant cells. There were coronary arterial lesions of the character seen in the hearts of rheumatic fever patients. Panarteritis of the so-called "allergic" or periarteritis nodosa type was, however, not present in these rabbits' hearts. Neither bacteria nor inclusion bodies were seen in these cardiac lesions. Noteworthy has been a distinct correlation between marked enlargement of

the adrenal cortex and the occurrence of myocardial granulomata in the rabbits dying, or sacrificed while sick, following the last of several cutaneous streptococcal infections. Several different sets of controls indicate that the experimental conditions apparently conducive to the induction of the lesions described were successive focal lesions caused by group A streptococci of different serological types.

From the results of these experiments it would seem unwise to assume, unreservedly, that rheumatic fever had been induced in these rabbits; but, on the other hand, to deny this possibility, in view of the data presented, would also be unjustified. Those investigators, notably Klinge and his collaborators [57] and Rich and his coworkers,[58] who have emphasized many points of similarity between the carditis seen in rabbits receiving one or more injections of foreign protein and that of rheumatic fever, have argued that these histopathological analogies indicate an "allergic factor" as being common to the two pathological states. It has been emphasized by Ehrich et al.,[59] however, that there are enough histological diversities in the two conditions to indicate that they are not strictly comparable. Many years ago, in discussing Klinge's investigations, Aschoff [60] emphasized the hazard of attempting to establish the causation or essential nature of a disease by comparing one or two points of analogy with those of another disease. He insisted, that to prove a common causative factor in two such comparable conditions, a single common stimulus must be employed.

In investigating a possible etiological rôle of suspected microörganisms in a given disease and in planning a working hypothesis to test whether, and how, these microörganisms may induce this disease experimentally, it would seem quite important to duplicate, as closely as possible, the particular chain of circumstances under which these agents appear to induce the typical disease in nature. In the earlier part of this lecture are outlined the data obtained from applying current knowledge of group A streptococci and their antigenic components to the bacteriological and immunological studies of rheumatic fever patients; in the latter part is summarized how these data have been utilized in studying experimental streptococcal infections in rabbits. Eventually, by imposing on these animals infectious conditions approximately similar to those observed among rheumatic fever patients, there has been induced a histopathological picture in their hearts closely resembling that of human rheumatic carditis. The small proportion of infected rabbits showing this picture roughly approximated the relative frequency of rheumatic fever encountered among patients infected with group A streptococci.

On the basis of these investigations and of the hypothesis employed in planning them, there seems to be furnished additional support to the theory that group A streptococci are important factors in the pathogenesis of rheumatic fever; and the investigations also indicate how these microörganisms may act in giving rise to this disease.

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SODIUM SUCCINATE—AN ANALEPTIC FOR BARBITURATE POISONING IN MAN *

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THE barbiturates, next to carbon monoxide, are the most frequent source of poisoning, both suicidal and accidental.[2] This may well be attributable to the widespread use of the barbiturate drugs [1] as evidenced by the fact that in 1945, alone, over 290 tons of this one group of hypnotics were produced.

This paper reports an investigation of the effects of a new analeptic agent, sodium succinate, in the treatment of poisoning with barbituric acid compounds.

The present and generally accepted treatment of barbiturate poisoning [3] consists of one or all of the following procedures with, possibly, others: (a) Administration of oxygen, alone or in combination with carbon dioxide, to combat anoxia; (b) administration of intravenous fluids, to increase, supposedly, kidney filtration and thereby remove the barbiturate, at an increased rate; (c) gastric lavage, employed very early, in an attempt to remove the depressant drug, provided it were ingested; and (d) probably the most outstanding of all, the use of various convulsant drugs given intravenously. Picrotoxin, an outstanding example of the convulsants, first came into general usage in 1936. Since that time, it has been the drug most commonly used in the treatment of barbiturate poisoning.[4]

One may accept readily the use of oxygen and certain intravenous fluids as supportive therapy. However, gastric lavage should be used rarely, if ever, on a comatose patient with suspected barbiturate poisoning, because of the danger of inducing vomiting and consequent aspiration of stomach contents.

The use of convulsant drugs in the treatment of barbiturate poisoning while justified in critical situations is not without danger. In accidental and, especially, in suicidal barbiturate poisoning, exact dosage and type of barbiturate consumed is rarely known; therefore, a safe dosage of convulsant is difficult to determine. It has been stated that should a convulsion develop during the use of a convulsant drug, the convulsion may be controlled easily by giving more barbiturate.[4] This procedure could lead to disastrous results. Certain convulsants, given in subconvulsant doses, may prolong the later stages of recovery from the effects of hypnotics, and this secondary depression may be accompanied by pulmonary edema.[5] Hence there is possibility of underdosage, as well as overdosage.

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Unexplained coma, or deep narcosis, may be assumed mistakenly to be the result of barbiturates. Radical therapy with convulsant drugs in such an instance diminishes the patient's chance for recovery. Unfortunately, the "do-something" attitude is usually present when a possible suicide or accidental poisoning is concerned and accurate diagnostic procedures may be sidestepped. In most cases of supposed barbiturate poisoning, until diagnostic tests have been made, symptomatic treatment, especially the maintenance of an adequate airway, may be, not only the safest, but also the wisest treatment. When compared with the large number of so-called "barbiturate poisonings," death from the barbiturates, per se, is comparatively rare. Some of the deaths that do occur must be attributed to idiosyncrasies, because of the small dosage of drug consumed. Some deaths are undoubtedly the result of treatment. Many, possibly most, fatalities are due to serious complications in the respiratory tract.

If some drug were available that could be used safely in unproved as well as proved cases of so-called "barbiturate poisoning," it should have an important place in the armamentarium of most physicians. Sodium succinate is, apparently, so qualified.

The possibility of using sodium succinate as an antidote for barbiturate poisoning was suggested by Soskin and Taubenhaus in 1943.[6] Their suggestion was based primarily on animal (rat and dog) experimentation; however, they did report that in a case of combined barbiturate and picrotoxin poisoning in a human the intravenous use of sodium succinate "appeared to be of benefit." The patient recovered. They did not imply that this single case proved "anything," but they did state that it indicated the desirability for further investigation on human material.

Interest in their findings was shown by the appearance of subsequent reports on the effect of succinate in barbiturate poisoning in several controlled series with animals, and recently a preliminary [7] and a detailed report [8] on a controlled clinical series.

Review of the literature covering the use of sodium succinate in the treatment of experimental barbiturate poisoning in laboratory animals [8] leaves one in confusion regarding the existence of any analeptic quality in this agent.

Material

A 30 per cent aqueous solution of the hydrated salt of sodium succinate (disodium succinate hexahydrate)* was used in the investigation to be reported. Sodium succinate is a salt of succinic acid, one of a group of four-carbon dicarboxylic acids. The actual mode and site of action of sodium succinate, as an analeptic, in barbiturate poisoning has not been determined. It is probable that this action is intimately concerned with tissue respiration and the rôles of succinoxidase and probably cytochrome oxidase. The pos-

* This solution was supplied for the purpose of this investigation under the name "Soduxin" by Brewer and Company of Worcester, Massachusetts.

sibility of a reflex mechanism, based on the hypertonicity of the agent used, has been considered. A brief discussion relative to the possible mode of action of succinate has been presented elsewhere.[2]

Sodium succinate is a hexahydrated salt; therefore, the actual concentration of the solution used was about 18 per cent, rather than 30 per cent. This solution is stable at normal room temperatures (20° to 25° C.) but it becomes less effective or completely ineffective, as an analeptic, if allowed to remain at higher temperatures.

In an earlier report,[3] a series of 70 clinical cases that had received sodium succinate after Pentothal Sodium anesthesia ("controlled barbiturate poisoning") was compared, with a similar series that received only Pentothal. The results of that investigation demonstrated that sodium succinate when used, according to a simple procedure, was definitely effective in shortening the sleeping times of the cases in the experimental series. The results were often quite dramatic.

The purpose of the present investigation was to evaluate the effectiveness of sodium succinate used in man for the treatment of "uncontrolled" (that is, suicidal or accidental) barbiturate poisoning. The effect of the drug in 15 cases was studied. All subjects in this investigation had, or were diagnosed tentatively as having, "barbiturate poisoning"—produced accidentally *or* with suicidal intent. All were from rural areas. They were treated in a community hospital or in the home.

Method

There was no specific preparation of the barbiturate poisoning cases previous to their initial treatment with sodium succinate. Manual or mechanical removal of any obstruction to the airway was a routine. When indicated, an artificial, pharyngeal or endotracheal, airway was introduced. (The endotracheal tube facilitates proper cleaning of the tracheo-bronchial tree.) The recumbent patient was placed usually in a slightly head-down position. Gastric lavage was *never* used.

Sodium succinate was given intravenously, immediately following the routine, preliminary procedures, just mentioned. The first 3 to 5 c.c. of succinate solution were injected rapidly—usually at the rate of 1 c.c. per second. The remainder of any indicated quantity was given more slowly. There is no fixed dose for sodium succinate; it should be given intermittently as indicated.[2]

Injection was delayed for 10 to 20 seconds after the initial dose. Typically, patients coughed once or twice during that brief pause. The cough was taken as a sign of adequate initial dose. If no cough were produced by the first dose, the dose was repeated. Unanesthetized human volunteers have described the subjective stimulus for the cough as being similar to that sensation which one experiences on taking a large drink of what he expects to be straight gingerale, but which proves to be straight whiskey!

Following the cough and a typical increase in depth of respiration, a crimson flush (the "succinate flush") appeared in the blush areas.

Intravenous injection of succinate was continued until definite analeptic responses were evident, such as groaning, voluntary movement of body, opening of eyes, etc. Occasionally, 30 to 45 grams (100 to 150 c.c.) of the agent were given within 15 to 20 minutes. Dosages employed in each of the 15 cases are indicated in table 1.

Data

This report is based on observations in 15 cases of "barbiturate poisoning" treated with sodium succinate. There were no deaths—from poisoning or therapy. In 14 of these 15 cases, the causative agents were, wholly or in part, barbiturate acid compounds. Coma in the remaining case was believed, originally, to be due to a barbiturate, but later the responsible factor proved to be of physical origin. This case has been reported previously [3] but it will be repeated here, for an obvious purpose.

The "poisoning" drug and the number of cases concerned in this series were divided as follows (table 1): barbital ("Veronal"), two cases (No. 1, 3); phenobarbital ("Luminal"), two cases (No. 6, 10); amytal and the so-called "short-acting" [8] barbiturates, sodium amytal, pentobarbital sodium ("Nembutal") and "Seconal," seven cases (No. 4, 5, 7, 9, 11, 12, 13); and three cases (No. 8, 14, 15) of idiosyncrasy to, or overdosage of, Pentothal Sodium. Two of the group had taken a combination of things. There were five males and 10 females. The poisonings occurred in a period of about two years (1945 and 1946). These 15 cases are not a true indication of the number of so-called "barbiturate poisoning" cases that were seen during that time, but they were cases for whom an analeptic agent seemed indicated.

Two of the males (aged 60 and 66) had been markedly depressed by relatively small doses of Pentothal Sodium; each received about 0.5 gram in a 2.5 per cent solution, given over a relatively long period. Their depression was due, possibly, to poor physical condition and age, either of which may be a factor in sensitivity to Pentothal Sodium, but from comparison with similar cases, it appeared to have been the result of idiosyncrasy.

Another male, aged 61, received 1.3 grams of Pentothal in 15 minutes. Obviously, this was a large dose, but apparently it was necessary for the patient and the type of surgical operation concerned.

One male (No. 1) had been hospitalized formerly in a psychiatric institution because of previous attempts at suicide.

The last male (No. 13) of this series was a pharmacist who had taken "Seconal" in repeated doses "for relief of pain."

Six of the 10 females had taken barbiturates with suicidal intent. One of the others (No. 10), although not an epileptic, had taken more than six grains (0.39 gram) of phenobarbital daily in the previous 10 years. She was hospitalized because of convulsions alternating with coma. Barbiturates had been denied the patient previous to admission. She was demonstrating withdrawal signs of chronic barbiturate poisoning.

One case (No. 6), a 64 year old woman, had fallen downstairs several days before admission. Her only complaint to her family physician, relative to her fall, had been

TABLE I

Sodium Succinate—An Analeptic for Barbiturate Poisoning in Man

Identification	No.	Sex	Age	Type and Dosage of Barbiturate	Narcosis Time			Dosage of Sodium Succinate 3 gm./10 c.c.	Narcosis Time after Succinate Therapy	T.N.T.	Comments
					Outside Hospital	Inside Hospital	Total N.T.				
42438 P. H.	1	M	64	Barbital gr. 125 (8.3 grams)	5°	42°	47°	30 gm. (100 c.c.)	15′ opened eyes 45′ oriented—to status quo	47°45′	Known psychopath. Negativism and bed boards on awakening.
42903 C. T.	2	F	56	None (cerebrovascular accident)	10°	3°	13°	20 gm. (200 c.c. of 10%)	30′	14°	? of cerebrovascular accident before succinate therapy. Later proved by autopsy.
47840 L. R.	3	F	58	Barbital gr. 150 (10 gm.) Nembutal, 4.5 gr.	28+1°	1°	30°	30 gm. (100 c.c.)	5″ cough 2°35′ oriented	32–33°	Nembutal taken with one ounce of elixir of phenobarbital. Chin relaxed on admission.
41613 P. C.	4	F	23	Seconal, gr. 19.5 (1.3 gm.)	9–10°	15′	9–10°	42 gm. (140 c.c. 3°)	4° oriented	14°	Pupils exhibit reverse reaction to light, for first 30′ of succinate therapy.
39088 A. H.	5	F	66	Nembutal, gr. 13.5 (0.9 gm.) Capritol (?)	2°30′	1°	3°30′	4.5 gm. (15 c.c.)	10″ cough 15′ turning 20′ oriented	4°	(Amyotrophic lat. sclerosis)
42225 R. D.	6	F	64	Phenobarbital (repeated doses) Amt.?	3 days ?	1 day	4 days	4.5 gm. (15 c.c.)	24° oriented	5 days	Pt. had fallen down stairs. Phenobarb. given for relief of physical discomfort (pain!) Memory loss after first or second dose. "Thanks" for reviving.
42226 A. P.	7	F	45	Amytal (amount ?)	10°	7°	17°	6 gm. (20 c.c.)	10″ cough 1′30″ groan 3′ opened eyes	17°3′	Told family she had taken "sleeping pills." They didn't believe her for 10 hours.
50427 A. H.	8	M	66	Pentothal (2.5%) (450 mg. in 15′) for surg.	—	7°	7°	3 gm. (10 c.c.)	10″ cough 5′ tingling in face	7°5′	Normal B. P. 110/70. Before succinate 90/50. After 150/90; then in 5′ to 110/70.
46560 M. S. O.	9	F	48	Sod. amytal, gr. 6 (0.4 gm.)	8°	1°	9°	3 gm. (10 c.c.)	20″ cough 20′ oriented	9°21′	Possible idiosyncrasy to drug or memory loss by pt. re amt. of amytal taken.
48752 P. N.	10	F	40	Phenobarbital, gr. 6.75 daily for 10 years	Semi-com.	Semi-com.	Semi-com.	3 gm. (10 c.c.)	1′ (increased depth of respiration)	1°	Pt. exhibiting withdrawal symptoms of chronic barbital poisoning.
45863 D. M.	11	F	3	Nembutal, gr. 4½ (0.3 gm.); Phenobarb.; nail polish remover.	2°45″	3°	5°45′	3 gm. (10 c.c.) Initial 15 gm. (50 c.c.) Total in 3°	2′ cough 3° oriented	7–8°	Unknown amt. of phenobarb. taken. One ounce of nail polish remover (acetone).
598 A. C.	12	F	38	Nembutal, gr. 15 (1 gm.)	30′	Not in Hosp.	30′	6 gm. (20 c.c.)	15″ cough 1′ talking	31′	Not admitted to hospital.
47227 L. Y.	13	M	63	Seconal, gr. 27 (1.8 gm.) Divided doses.	10°	20′	10°20′	6 gm. (20 c.c.) Initial 21 gm. (70 c.c.) Total	10″ cough 2° oriented	12°30′	Pharmacist. Seconal taken for relief of pain (self treatment). Could be roused but was disoriented. Memory loss.
30487	14	M	61	Pentothal (2.5%) 55 c.c. (1375 mg.) given in 15″ for surgery.	—	20′	20′	2.8 gm. (9 c.c.) Initial 6 gm. (20 c.c.) Total	5′ groaning 30′ moving head and body	50′	Pt. in laryngospasm when succinate given. This stopped in 20″.
36718	15	M	60	Pentothal (2.5%) (550 mg.) For surgery.	—	25′	25′	6 gm. (20 c.c.)	1′ cough 5′ eyes open	30′	Pupils pin point before succinate, dilated after 3 c.c.

° equals hour. ′ equals minute. ″ equals second.

"sleeplessness because of little aches and pains." Phenobarbital had been prescribed for this complaint. The initial dose of one-half grain (0.03 gram) was "to be repeated once, if necessary." After recovery, this patient remembered, vaguely, that she had taken "one or two more tablets." However, when her family discovered that she could not be aroused, they also noted the empty medicine box. From the *patient's* standpoint, this was a case of accidental poisoning.

A three-year old girl (No. 11) had taken a combination of "Luminal and Nembutal-C tablets" with an ounce of fingernail polish remover as a "chaser" before admission to the hospital.

The remaining female of the series was a 56-year old housewife who was brought to the hospital because of probable barbiturate poisoning. She had been found asleep in her bed late in the morning. When her son could not arouse her, he became alarmed and called their family physician. On admission to the hospital, she was described as having been "found in a comatose state and with absent reflexes." One physician made an admitting diagnosis of "cerebro-vascular accident and cardiac failure with passive congestion." Another physician wrote: "probable barbiturate poisoning." Shortly after these temporary diagnoses were made, a relative of the patient appeared with a box containing, what he described as "sleeping pills." The partially filled box had been found in the patient's home under her bed. Admitting diagnoses of the two physicians were not changed. An anesthesia service consultation was requested. These physicians were aware of this service's interest in the use of succinate on this type of case, that is, a case in coma of questionable etiology.

Two hours after admission of the patient, physical findings were unchanged; notably, knee jerks and ankle jerks were still absent, and it was necessary to hold the patient's jaw in order to maintain an adequate airway. At this time, a solution containing 10 per cent sodium succinate and 5 per cent dextrose was started by intravenous clysis at a rate of 20 drops (1.6 c.c.) per minute. Twenty minutes later, 30 c.c. of this solution were injected, as a single dose, in one minute. In the next minute the patient opened her eyes, responded to her name by groaning, and moved her left arm and leg in an attempt to turn. Knee jerk on the left was normal, but absent on the right. There was a right-sided flaccid hemiplegia.

Dilute (10 per cent) succinate solution was given at the rate of about 75 drops per minute, for the next 30 minutes, or until a total of 200 c.c. had been taken.

The patient remained in a semi-conscious state during the next three hours and could be aroused easily throughout the remainder of the night (about six hours).

She died two days later. The findings at autopsy were "arteriosclerosis of cerebral vessels" and "recent infarct of left cerebrum." That this patient *was*, at the time of treatment with succinate, suffering from cerebral anoxia is probable. That sodium succinate *did* relieve, in some way, at least *temporarily* and *in part*, the anoxemic state is suggested by events. That the case was one of barbiturate poisoning is improbable. And—although the patient was not cured with the agent used—certainly, the use of any convulsant drug was contraindicated in this case and would be in others of similar type. The "sleeping pills" contained, principally, an ephedrine-like compound.

Three cases, typical of the series investigated, will be presented. The first is that of a widow, aged 58, who was admitted to the hospital after a total narcosis time (T.N.T.), elsewhere, of about 30 hours. During that time, breathing was reported as having been "adequate," but she had been flaccid and could not be aroused.

Her blood pressure on admission was 100 mm. Hg systolic and 60 mm. diastolic. Radial pulse rate was 80 per minute and respiratory rate was 16 per minute. Breathing was very shallow. It was necessary to support her lower jaw to provide an adequate airway. Removal of a moderate amount of tenacious mucus from the oropharynx improved breathing.

While the patient was being examined, 5 c.c. of 30 per cent sodium succinate were given rapidly, by vein. After five seconds, the patient coughed and moved her right leg. Systolic blood pressure increased by 10 mm.

Three minutes after the initial injection, an additional 10 c.c. of succinate solution were given rapidly. The immediate effect was a marked increase in depth of respiration without any remarkable change in rate. The blood pressure was then 120/80.

During the first 10 minutes of therapy, the patient received 50 c.c. of succinate solution. (This was equivalent to 15 grams of hydrated sodium succinate or 9 grams of the anhydrous form.) Following this dose, the eyelid reflex was present and she was moving her legs. A crimson flush was present in the blush areas.

An intravenous clysis of 10 per cent succinate and 5 per cent glucose was started at a slow drip-rate. Fifteen minutes later, the patient was slightly cyanotic. A large amount of thick, tenacious mucus was removed from the pharynx; the infusion rate was increased; and, for five minutes, 100 per cent oxygen was given by face mask.

Two hours and 35 minutes after the start of succinate therapy, the patient was well oriented and talking coherently. She stated that she had taken "4½ grains (0.3 gram) of Nembutal, and one ounce of elixir of phenobarbital." *This,* certainly, was ***not an excessive dose,*** especially considering the fact that, according to her home physician, she was not abnormally susceptible to the usual effects of these drugs; however, two hours later, she "remembered" also 30 five-grain barbital tablets (150 grains or 10 grams) that she had taken with the other hypnotics.

This woman received 100 c.c. of 30 per cent sodium succinate (30 grams of the hydrous salt) in two hours and 35 minutes.

A three-year-old girl, who, at the time of admission, was comatose, moderately flaccid, and unresponsive to normally painful stimuli, with acetone-like breath and rapid respirations, had signs of pulmonary edema on the right. The child had no history of diabetes and, obviously, was not undernourished.

Total narcosis time before admission was indefinite, but it was not more than two and three-quarters hours.

The history of this case previous to admission was essentially as follows: The patient's five-month-old brother had been, supposedly, having his mid-morning nap. Their mother had been busy with housework until she went into the baby's room to get something. There, she found the patient "sound asleep on the floor," and the baby "wide awake in his crib." Several different types of tablets and pills were scattered on the floor; also, a new, four-ounce bottle of nail polish remover was open and only three-fourths full. The family physician was called and the patient was brought to the hospital.

Three hours after admission there had been no appreciable change in the patient's general condition. The respiratory rate remained rapid and shallow, and the child continued to be comatose and unresponsive.

At this time, 10 c.c. of sodium succinate (30 per cent) were given, in two minutes. During the initial course of the injection, the patient demonstrated the typical cough, following which she swallowed several times. A "succinate flush" appeared on her face and arms. Respirations became deeper.

Two and one-half hours later, an intravenous clysis of 10 per cent succinate and 5 per cent glucose in water was started.

Within the next half-hour, the succinate flush covered practically her entire body. The patient reacted to painful stimuli and opened her eyes, when requested to do so.

Although ataxic, she was well oriented in the following hour and asked for "a good lunch and a big glass of milk." She got both and consumed both. This was less

than five hours after admission, or a possible total narcosis time of seven to eight hours.

While the child was eating this lunch, specimens of drugs, known to have been present in the mother's bedroom, were spread on a tray by the patient's bed. This was placed in a conspicuous position before her, as she told how "bad Baby Brother" (all five months of him!) had "jumped out of his crib" and "spread medicine all 'round.'" She continued by saying that he had eaten "three of these" (Nembutal-C, 4½ grain or 0.3 gram, total) and "lots of those" (phenobarbital, unknown amount). She concluded her revelations with: "and then he took a big drink of the new nail polish!" Actually, it was nail polish remover, rather than polish, and "Baby Brother" was, in no way, involved. Chemical analysis confirmed the belief that this particular nail polish remover was principally acetone.

This young patient received 50 c.c. of sodium succinate (equivalent to 18 grams of the hydrous salt) in three hours. The initial dose was 3 grams, or 10 c.c. of the stock solution, given in two minutes. The remainder was given as a 10 per cent solution combined with 5 per cent glucose.

The remaining case to be described was that of a male, aged 64, who had been diagnosed previously as being psychopathic. It was known that he had taken 125 grains (8.1 grams) of barbital. For the depression that followed, he had been given 16 c.c. of 0.3 per cent picrotoxin, by his local physician, 30 minutes before hospital admission. This had produced a convulsion. However, at the time of admission he was again in deep narcosis.

This patient was given common supportive treatment during the first 24 hours in the hospital. There was no improvement in his general condition. In the twenty-fifth hour, he was given 100 c.c. of sodium succinate solution (equivalent to 30 grams of sodium succinate). Within 15 minutes, he responded and, within an hour, he was as well oriented, allegedly, as he had been before taking barbital. There were no convulsions, and he did not go to sleep again for several hours. In fact, it was necessary to put side boards on his bed, because he insisted on getting out and wandering around the ward.

Discussion

In order that the effects of therapy shall not be more harmful than the condition being treated, there is an ever-present need for marked carefulness in the treatment of barbiturate poisoning and the need is even greater in the treatment of *supposed or assumed* "barbiturate poisoning." From this and previous investigations, by the author, on man, it appears that sodium succinate may be used safely in any stage of narcosis or in the quite awake individual.[7] It has been demonstrated many times that the analeptic effect of succinate on man is directly related to the depth of narcosis, that is, the greater the need, the more marked is the effect—or, the less the need, the less will be the effect.

In relation to this finding, it is interesting to note an observation made by Banga, on tissue cultures, as stated by Elliott: "Banga showed that it was not easy to remove all the four-carbon (dicarboxylic) acids from tissue. It is, therefore, possible that when added four-carbon dicarboxylic acids have little effect on the respiration of tissues, these substances may already be present in the tissues in such amounts that their concentration is not a limiting factor of the respiration rate.[10]

In several hundred administrations of sodium succinate to man, under various conditions and for various indications, there have never been visible convulsions nor production of excitement, beyond the *status quo* of the subjects concerned.

It has been stated that "patients with barbiturate poisoning fall into four groups, two of which recover and the remaining two do not. The first is the group of patients who recover without any treatment. All they require is general nursing. The second is the group of patients who die regardless of how intensive and expert the treatment is. They have simply taken so large a dose that no antidote or method of treatment can save them. The third group embraces those patients who recover only because of expert management; without the most effective measures most frequently applied they would succumb. The fourth embraces those patients who die because of the treatment."[2] Sodium succinate can be a factor in eliminating the last group and, probably, the second.

It may be helpful to know the amount of barbiturate a patient has taken, but this information is frequently inaccurate. It is, however, well to remember that adults are almost certain to recover, without specific treatment, from oral doses of the order of 1 or 2 grams of any of the commonly used barbiturates. The fatal dose is sometimes stated as being, in general, 15 to 30 times the therapeutic dose. It has been said that the dose of barbital which is nearly always fatal is about 10 grams, and that of phenobarbital, from 6 to 8 grams.[9] However, there are so many factors that may contribute to the depressing effect of the barbiturates, such as physical and mental fatigue, a very recent hot bath, analgesic drugs, etc., that discussions concerning any fixed, or even nearly fixed, so-called "fatal dose" have little, if any, value. Every case of barbiturate poisoning should be treated as an entity—regardless of drug taken, or supposedly taken. The greatest foe in the treatment of barbiturate poisoning is anoxia. The greatest foe in recovery from barbiturate poisoning may be the type of treatment employed.

A few years ago, before the use of succinate, a 17-year-old girl, who had taken an indefinite amount of phenobarbital, was admitted to our hospital. The quantity of drug concerned was estimated, by the referring physician, to be between 150 and 200 grains (10 to 13 grams). At the hospital, it was estimated that she would sleep for a week. She did.

During that entire week her position was changed every half hour, day and night, side to side, foot of bed elevated, then head of bed elevated. Some of the convulsant drugs were used, but only in relatively small doses. Supportive therapy was the main course of treatment. The maintenance of fluid, electrolyte and protein balances became a complicated problem. During the last four days of the week, a constant vigil was necessary. In order to maintain an adequate airway, it was necessary to bronchoscope the patient two or three times to remove thick, tenacious mucus from the tracheobronchial tree. Recovery was finally complete, and there were no apparent mental changes. However, it was a very exhausting ordeal, especially from the nursing standpoint. Without conscientious nursing care, recovery for this case would have been impossible. It is for cases of this type, especially, that succinate is indicated.

There are many cases of *so-called* "barbiturate poisoning" that require no specific treatment beyond adequate supportive care. It is well known that many patients, in certain depressive states, receive considerable benefit from prolonged sleep of 24 to 48 hours, or, possibly, longer. It is conceivable that some suicide patients may actually benefit by their self-poisoning with barbiturates *if* they are adequately protected against anoxia; however, the possibility cannot be relied upon.

Summary

The frequency of over-indulgence, by the general public, in the misuse of the barbituric acid compounds, that is, self-treatment—to the extent of addiction and attempted self-destruction—has been reiterated.

Generally accepted, supportive treatment of barbiturate poisoning has been reviewed. The difficulty involved in making a diagnosis of true "barbiturate poisoning" has been restated. The fact that making this diagnosis is often a time-consuming procedure has been emphasized.

A method for the use of sodium succinate in the treatment of comatose patients, having, or suspected of having, barbiturate poisoning, has been presented.

Fourteen cases of true barbiturate poisoning, that were treated with sodium succinate for the purpose of investigating its analeptic effect, have been reported. Three of these were presented in detail. There were no deaths in the series.

One case of suspected barbiturate poisoning, that later proved to be a case of cerebro-vascular accident, in coma, was presented. This case was reported for the purpose of indicating the possibility of harmful effects that may result from the use of convulsant drugs, in the treatment of a patient in coma of unknown etiology.

The author has had no untoward effects from the use of sodium succinate in man. Pulmonary edema has been reported in small animals, following rapid injection of this agent. It has not been observed in man, although large quantities have been injected, as rapidly as possible, through a 20-gauge needle.

The importance of treating each case of barbiturate poisoning as an entity has been stated.

Conclusion

Sodium succinate is indicated for the treatment of "suspected" or "probable," as well as actual, barbiturate poisoning in man. This indication for succinate is based on the following: (1) its analeptic effect without, apparently, the possibility of producing convulsions, (2) its non-toxicity, and (3) its demonstrated property of aiding in the reëstablishment of the status quo in the poisoned patient.

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LOWER NEPHRON SYNDROME*

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The relatively high frequency with which the lower nephron syndrome, a highly fatal disease state, is observed clinically makes imperative a thorough acquaintance with the clinical picture. The syndrome is particularly common during wartime, when man receives bodily injury.[15, 16, 61, 74] It may be produced by transfusion reactions[3, 24, 28, 31, 45]; crushing injury,[16, 30, 33, 47, 61, 83] burns,[38, 48, 63, 82] heat stroke,[88] blackwater fever,[41, 66, 105, 108] toxemia of pregnancy, uteroplacental damage,[109] certain types of intoxications,[27, 34, 36, 87, 101] such as sulfonamide reactions,[42, 43, 62, 94] and other conditions.[46, 57, 65, 70, 84, 110] The high case fatality rate accentuates the need for a thorough knowledge of the disease, so that it may be managed properly and preventive measures may be instituted to reduce its incidence. It is the purpose of this presentation to review briefly the problem of the lower nephron syndrome, including the clinical picture, phases of its mechanism, prevention, and management.

A historical discussion of the lower nephron syndrome would have no particular value here. It is of interest, however, to note that the first papers on this subject were published in the German literature following the first World War.[44, 52, 74, 79, 90] Nevertheless, relatively little attention was given to the syndrome, despite the fact that a large number of such patients was encountered during battle. Probably the most interesting and important early paper was that published by Minami in 1923.[74] He described the clinical picture, indicated the nature of the damage, its relationship to crushing injuries, and also comprehensively presented the pathologic manifestations. Other papers include those of Ganter,[44] Landsberg and Gnoinski,[58] and Rosenak and Siwon,[90] which suggested the possible value of peritoneal lavage in the management of temporary acute renal damage.

Except for the reports on blackwater fever, transfusion reactions, mercurial, arsenic, and uranium poisoning, and toxemias of pregnancy, relatively little was published about the lower nephron syndrome before World War II. During the recent bombing of London, however, many English civilians received crushing injuries which presented a rather characteristic clinical picture. As a result of a study of these patients, Bywaters and his associates described the picture of the lower nephron syndrome again.[15-22] Various designations were employed: "crushing injury," "ischemic muscle necrosis with renal injury," "crush syndrome," "traumatic anuria," and "compression syndrome." A series of excellent papers by Bywaters and his group followed in rapid succession.

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As Bywaters [15] pointed out, the disease is really not new. Similar cases had been encountered at least as early as 1909 by Colmers,[23] though they were not recognized. In 1946 Lucké [61] reported an excellent study of observations made on 538 fatal cases of "lower nephron nephrosis," as he called it.

Increased interest in and knowledge of the lower nephron syndrome and some of the acute anurias has resulted in more frequent use of the artificial kidney [55, 56] and other methods for the removal of toxic elements circulating in the blood of the anuric patient. Numerous papers have been published on the subject within the last few years and many more are sure to follow, especially since the possible clinical value of such procedures has been definitely realized.

The Clinical Picture

Before the more fundamental aspects of the lower nephron syndrome are discussed, it is advisable to review the clinical picture.[16, 17, 61] As stated previously, the *causative* agent varies widely. The patient suffering from a crushing injury which produces lower nephron nephrosis presents a history of having been pinned by heavy beams or pieces of masonry in such a manner that a considerable amount of tissue has been crushed. He has usually remained under the crushing force for several hours. As a rule, he appears to be in good condition soon after release except for wounds and local injuries, such as fractures and contusions. However, in a few hours he begins to show evidences of edema and slight oozing and hemorrhage into the injured tissues and from the wounds. He then passes quickly into the *first phase of shock*, which is considered by many to be due to loss of plasma through damaged capillary walls into the tissue spaces of the injured areas. These areas become extremely swollen, and the skin becomes shiny. Evidences of necrosis with bleb formation may appear. Loss of fluid into the tissue spaces results in hemoconcentration, evidenced by an increase in hemoglobin, hematocrit and erythrocyte count. During this phase of shock the skin tends to be pale, cold and moist, although the blood pressure generally remains essentially normal, apparently because of compensatory vasoconstriction. Occasionally when this vasoconstriction is not maintained, there follows a rapid drop in blood pressure, with the development of the *second phase of shock*. If plasma or fluids are administered at this time, the blood pressure will return to normal. With inadequate therapy shock may become irreversible.

The patient tends to show evidences of *anxiety*. The first or second samples of *urine* passed following the injury are noted to be bloody and to contain pigment suggestive of hemoglobin or altered hemoglobin. The urine also contains albumin, creatine, granular casts and pigment granules, which sometimes resemble intact erythrocytes. It is usually highly acid, with a pH of 4.6 to 6.0. The urine volume remains low and may even approach anuria. Oliguria continues despite fluid intake or any form of therapy. The specific gravity tends to become fixed at 1.010, correction having been made for the protein content.

In the meantime, the damaged tissue, as for example, the limbs or trunk, becomes so swollen, hard and tense that digital indentations cannot be readily made. This swelling usually progresses for the first four or five days. Petechial hemorrhages, erythematous wheals, and large blisters are usually noted at points of pressure over the injured structures and extend to adjacent areas. There may be patchy anesthesia of the involved area, probably related to damage of terminal nerve fibers. Paralysis of varying severity and extent generally develops. Arterial pulsations in the peripheral parts may be absent and the part may be cold and pale. Gangrene may occur.

The patient becomes apathetic, with alternating phases of anxiety and extreme apprehension. He is usually aware of the severity of his disease. About this time vomiting may be prominent; this is an important aspect of the manifestations because of its relationship to dehydration, malnutrition and disturbances in electrolyte balance. Blood pressure usually rises gradually above the previous or normal level.

Changes in chemical composition of the blood become evident at this stage. There is an accumulation of urea, potassium and phosphate in the blood; the carbon dioxide combining power progressively falls; and occasionally the blood chloride tends to decline in concentration, probably because of inability of the tubules to reabsorb chloride. The patient often experiences pain in the renal region, which is thought to be due to swelling of the kidneys with stretching of the capsule. The renal pain has been responsible for abdominal operations, performed erroneously in search of an acute abdominal operative state.

The end of the first week is usually the critical period. If the patient recovers, there is sudden diuresis, following which urinary output gradually rises to extremely high levels. Blood urea level falls, urea clearance improves, and tubular function shows evidences of returning to normal. During the recovery period, granular epithelial casts may be noted, replacing the pigment casts and erythrocyte casts present during the early phases of the disease. As a result of the pressure necrosis produced by crushing, damaged areas of skin, muscle and other tissues begin to slough. Severe infection may develop. With recovery, local fibrosis may become extensive and produce disturbances resembling Volkmann's ischemic contractures.

In some of the more severely injured patients cardiac irregularities may be noted at the critical period, and extreme electrocardiographic changes, particularly evident in the S–T segment and the T waves, begin to appear. The latter resemble changes described for potassium poisoning or those produced experimentally by intravenous administration of potassium. Though the potassium level may be greatly increased during this period, it is not yet known whether the levels attained in the lower nephron syndrome are sufficient to explain the electrocardiographic manifestations. Furthermore, potassium metabolism and the physiologic interrelationship of intra- and extracellular potassium are not well understood. It is well

known that damage to cells results in an escape of potassium into intercellular spaces.

If diuresis continues and if renal function progressively improves, the patient will make an apparently uneventful recovery. However, should diuresis fail to develop, there will ensue a continuous downward course, characterized by increasingly severe uremia with extreme mental disturbances, often terminating in coma. The patient often calls out with alarm, becomes pale, sweats profusely and the alae nasi become dilated. Death usually occurs suddenly, sometimes even within one or two minutes. He may recover from these episodes, only to be seized by another an hour or so later —one of them terminating fatally.

The general clinical pattern varies little with the responsible etiologic factors. The chief difference is in that phase of the patient's course concerned directly with the etiologic factors producing the entity. For example, in lower nephron nephrosis eventuating from a transfusion reaction there will be a history of administration of incompatible blood, followed by a severe chill and fever and then oliguria, hematuria, pigment and erythrocyte casts, and uremia, usually with ensuing death. Renal function decreases until the specific gravity is fixed at 1.010, and azotemia with retention of other toxic materials develops. In a patient who suffers a transfusion reaction, particularly postoperatively or as a result of treatment for an accident, various degrees of shock are liable to occur. *Shock* and *vomiting* are two of the associated manifestations which tend to precipitate or aggravate the oliguric state.[16, 61] It is interesting to note that in those patients who sustain such damage without the development of these two symptoms, the severity of the clinical state is not great.

When the lower nephron syndrome is produced by a reaction to sulfonamides, the patient has usually received the drug in the presence of an impaired cardiovascular system, such as congestive heart failure, or impaired renal function, with inadequate urinary output and often in the presence of acid urine.[14, 107] Hematuria occurs, associated with sulfonamide crystals in the urine and sometimes with pain over the renal regions. These patients, as a rule, do not manifest a shock-like state, although occasionally shock or peripheral circulatory collapse may occur, partially as a result of the reaction to the drug and partially as a result of the disease for which the drug was employed. The clinical course and general manifestations are essentially those described previously for the crush syndrome.

The clinical picture of the lower nephron syndrome also resembles that of the uteroplacental syndrome,[109] as encountered in postpartal sepsis or in criminal abortion with infection of the uterus. There is a difference in the clinical pattern due to the infection, but as far as the renal portion of the picture is concerned, it is essentially identical.

In summary, the clinical picture produced by the various disease states is modified in part by the etiologic factors concerned with the production of that

particular syndrome.[16, 17, 61] It is not possible to discuss each of the factors which might be responsible for the syndrome, but they are summarized briefly in the accompanying table (table 1) and references to them have been included. It is advisable to discuss briefly certain clinical manifestations frequently encountered in the lower nephron syndrome.

TABLE I

Etiologic Factors in 538 Fatal Cases Having the Characteristic Renal Lesions of Lower Nephron Nephrosis

(Under most of the groups listed are given the number of cases which received transfusions of blood, sulfonamides, or both, as therapeutic measures)

Battle Wounds (Gunshot, mine explosion, blast injury, severance of large blood vessel, etc.)	221
Crushing Injuries	46
Abdominal Operations (Carcinoma of colon, stomach, pancreas, etc. ruptured ulcer of duodenum or stomach; ruptured appendix, etc.)	36
Burns	48
Blood Transfusion Reaction (In cases of trauma, poisoning, infections, etc.)	45
Sulfonamide Intoxication (In cases of meningitis, pneumonia, other nontraumatic infections, infections associated with trauma, etc.)	47
Heat Stroke	19
Malaria (Falciparum); Blackwater Fever	14
Poisons (Arsenicals, carbon tetrachloride, alkali, carbon monoxide, alcohol (adulterated), isopropyl alcohol, phenol, photodeveloper, mussel, mushroom)	20
Hemolytic Anemia (Etiology undetermined)	4
Miscellaneous (Uteroplacental damage, eclampsia, acute pancreatitis, "shock" from various causes, etc.)	38

From Lucké, Balduin: Lower nephron nephrosis, Military Surgeon, 1946, xcix, 372.

(1) *Hypertension.* As stated previously, the blood pressure may decline, although generally it is maintained. Even if it falls to shock level, it rapidly returns to normal. In most patients observed, the fall has occurred on the first day, with restoration to normal on the second day of the disease, then a rise to 150 mm. Hg systolic and 90 mm. diastolic or slightly more on the third day. Thereafter this level is maintained or is even increased. The mechanisms for the changes in blood pressure are not known but apparently they are concerned with the usual factors associated with shock and renal dysfunction.

(2) *Edema.* There is usually a moderate amount of generalized edema. It is attributable to therapeutic procedures, such as parenteral administration of large amounts of fluids—an attempt on the part of the physician to force diuresis or to dilute the retained toxins. The edema in the local area injured by crushing or trauma is usually prominent, whereas that in the extremities and bases of the lungs is slight to moderate. Edema of the face is relatively uncommon except for slight puffiness; extreme facial edema is noted only in the more severely ill patients.

(3) *Uremia.* Uremia develops to some extent in all patients but is more severe in fatal cases. It is caused by the renal failure and is not due to other causes. However, such factors as repeated vomiting and disturbances in nutrition may contribute to the rate of production of azotemia and accumulation of toxic agents. Uremia begins within the first 24 to 48

hours, depending upon the rate of development of oliguria. However, the typical manifestations do not usually appear until the last two or three days of life. Vomiting and mental disturbances, such as irrationality, drowsiness and finally coma, are commonly associated symptoms. Convulsions are rare, as in any type of true uremia.

(4) *Fatality Rate.* The fatality rate is extremely high. Once the cardinal signs of oliguria, excretion of heme pigment, azotemia and hypertension develop, it reaches about 90 per cent. The course of the disease is relatively brief, and in fatal blood transfusion reactions the survival period is usually three to 10 days. In the crush syndrome death usually occurs by the end of the first week; most patients surviving eight to nine days recover. In one series [61] 74 per cent of the patients died within the first 48 hours. About 8 per cent of the patients who died have been reported to survive more than 12 days. It is not known whether death is due entirely to renal damage or in part to the precipitating cause itself, but it is quite likely that there are a number of contributing factors.

Pathology

The organic changes, other than those which occur at the primary site of injury by the etiologic agent, such as local tissue damage in the case of the crush syndrome or injury to the gastrointestinal tract in the case of mercurial poisoning, are largely confined to the kidneys.

Gross Appearance of the Kidneys. There are no pathognomonic gross manifestations of the lower nephron syndrome. The essential gross and microscopic manifestations are as follows [8, 15–17, 36, 61, 74, 77]: The kidneys are usually swollen and increased in weight, in some instances two or more times the normal weight. There has been no definite correlation between the size of the kidneys and the duration of the disease, although a certain amount of time is required for the swelling to develop. There is some suggestion that the increase in size of the kidneys after trauma or burns tends to be greater than that following nontraumatic conditions, such as transfusion reactions. Typically the kidney is somewhat soft, the capsule strips easily, the outer surface is pale, smooth and glistening, and a clear or slightly bloody fluid oozes from the cut surface. The cortex is widened and tends to bulge perceptibly. It is moist, pale and in sharp contrast to the dusky, somewhat cyanotic-appearing medulla. The striations are often greatly accentuated. A whitish stripe has been described in the inner aspect of the cortex.

Microscopic Findings. The histologic descriptions, including those of Bywaters and his group,[15–17] Minami,[74] Lucké [61] and Mallory,[69] have been summarized into four essentially distinct categories by Lucké [61]:

(1) There is degeneration and necrosis which involves somewhat selectively the lower part of the nephrons, that is, the thick portions of the loops of Henle and the distal convoluted tubules.

(2) Edema and inflammatory reactions develop in the interstitial spaces around the damaged and disintegrating tubules. These reactions are usually found where the tubular degeneration is most severe. Occasionally thrombosis of and severe damage to adjacent veins are seen. This interesting lesion is diagnostic.

(3) The heme casts of the lower portions of the tubules, including the collecting tubules, are characteristic.

(4) There are relatively slight or no histologic changes in the upper parts of the nephrons, that is, the glomeruli, proximal tubules and intermediate segments. Prominently and characteristically, the glomeruli are essentially normal in size and morphology. Although the vessels of the glomerular tufts are patent, the number of vessels seems to be reduced. Bowman's capsule and the space within it appear to be essentially normal, except that occasionally it may be dilated. The proximal tubule or the junction of the glomeruli with the tubules at the region of the Goormaghtigh body may exhibit mild histologic changes. This juxtaglomerular apparatus may be hypertrophied, with an increase in the granularity of the cells. The proximal convoluted tubules may appear essentially normal, although there is a tendency for the delicate brush-like border to be somewhat obliterated. There may be evidences of cloudy swelling, mild degeneration, and in rare cases, even necrosis. Within the lumen may be found precipitated material, which gives the appearance of concentrated proteins and stains with eosin. Heme casts are rarely observed at this level. This segment is readily damaged by mercury, uranium, or oxalates, but rarely is it damaged by the crushing injury in the lower nephron syndrome. This is also true to some extent in transfusion reaction, although in the latter there is usually more damage to the upper portion of the nephron than with crushing injuries.

The intermediate segment of the nephron is not ordinarily injured, although it may show changes such as described for the proximal portion, with accumulation of granular material and evidences of slight degeneration of epithelium.

The lower portion of the nephron, for which the term lower nephron nephrosis is applied, exhibits the greatest damage and seems to be selectively injured in the crush syndrome. Lower nephron damage is more apt to occur in cases of crush injury, burns, blood transfusion reactions, sulfonamide reactions, uteroplacental damage, and after excessive vomiting.

The morphologic changes observed microscopically are as follows: The damage occurs primarily in the tubular cells in the lower portion of the nephron. Degeneration varies from mild changes to complete patchy necrosis. Since the degeneration requires time to develop, its degree is relatively mild during the first 24 to 48 hours. Three to four days or more are required before definite evidences of degeneration appear. Since the lesions are characteristically patchy, there are scattered areas of desquamation of epithelium. Occasionally, pronounced lesions occur in the boundary zone, particularly at the point where the nephron is in close proximity to the vein.

These degenerative changes may result in bulging or even actual rupture of the necrotic portions into the veins. Diverticuli may be observed. Regeneration in various stages of development begins to make its appearance if survival time exceeds three or four days. There may be casting off of segments of epithelium with the growing of new cells beneath the dead lining. In the early stages the protoplasm tends to be basophilic and the nuclei stain intensely.

Healing takes place rapidly; if the patient survives 10 days, it is likely that the areas will be completely reëpithelized. Casts are the most characteristic and outstanding microscopic findings; they are usually of two kinds:

(1) Most conspicuous are the pigmented masses of heme substances which are found inspissated within the lumen of the lower portions of the nephrons. These are particularly highly developed when there is destruction of muscle and apparently have their origin from myohemoglobin or some of its derivatives. In hemolytic conditions, such as transfusion reactions, hemoglobin casts develop which are similar to the myoglobin casts following destruction of muscle. In unstained sections the casts have a reddish hue; when stained with hematoxylin and eosin, they are usually brownish or copper-colored, but the reaction for iron is negative.[61] The casts have a smooth and solid appearance and occasionally assume the form of spherules. They tend to accumulate in greatest numbers in the distal convoluted tubules but are larger in the wider collecting tubules. When they occur near thin-walled veins, they are apt to be prominent.

(2) Less conspicuous are those casts which are not pigmented and have the appearance of hyalin casts. They are stained faintly with eosin and look much like inspissated and coagulated protein material. Tending to occur in the region of the lower nephron where the injury is most severe, they give the impression of obstructing and blocking the flow of urine through the nephron.

Another interesting aspect of the microscopic pathologic changes is that seen in the interstitial tissues around the foci in the tubules showing extreme disintegration. Edema and inflammatory reactions are evident. There is an accumulation of inflammatory cells, particularly lymphocytes and histiocytes, whereas granulocytes are scanty and giant cells are rarely seen. Fibrosis usually develops at the end of a week, and if there is a great deal of destruction, scars appear. These areas may vary from relatively few to large numbers, depending upon the severity of the reaction. The interstitial changes are particularly pronounced in the boundary zone and at times in the cortex around the venous channels near the glomeruli. If necrosis is severe, casts are extruded into the stroma, producing local reactions. As stated previously, one of the interesting pathologic changes is found in the region of the large venous channel, especially in the boundary zone. There the veins are rather thin-walled and normally course near the renal tubules. When the tubules are damaged, the veins apparently bulge into the lumen.

In the presence of necrosis, the tubules may rupture into the vein and, spilling their contents therein, produce thrombosis. These thrombi rarely obstruct the vein. Remnants of epithelium may be found embedded in the thrombus. Veins are often infiltrated with inflammatory cells. Such venous lesions are usually encountered in patients who survive at least five days.

The collecting tubules rarely undergo any unusual degenerative changes. Their general appearance is normal, although heme casts are prominent at this level. They are often large and tend to fill and stretch the collecting tubules. Endothelial leukocytes may be found in this region. Some of the older lesions in patients surviving a long period of time show evidences of advanced degeneration of the heme compounds.

The number of nephrons involved, the extent of lesions, and evidences of obstruction vary considerably. Because of these histologic studies, it has been difficult for some to attribute oliguria primarily to obstruction.

The Mechanism of the Lower Nephron Syndrome

Although the exact mechanism for this syndrome is not known, certain facts have been established. Studies of Bywaters and his group concerned primarily with the crush syndrome indicate that crushed muscle undergoes characteristic changes within a short period of time. The muscle becomes ischemic due to direct compression which interferes with the blood supply and which probably is associated with sudden spasm and thrombosis, rupture or obstruction of the vessel. Following damage by crushing, the muscles become blanched, friable, and necrotic and resemble fish flesh. A sharp line of demarcation, which corresponds to the line of pressure, develops between the injured and uninjured areas. Muscles undergo various degrees of degeneration, varying from complete necrosis to almost normal tissue near the edge of the injury. Because of the edema, the muscles bulge through openings made in the fascia at operation. Some portions of the muscle may appear grossly normal, without too much pallor, but may still show isolated necrosis on microscopic section. This type of change is usually associated with arterial spasm, probably due to periarterial hemorrhage or rupture of the blood vessels from the crushing. Chemical studies of the necrotic muscle compared with undamaged muscle in the same individual, show that the damaged muscle has lost 75 per cent of its pigment, 75 per cent of the phosphorus, 66 per cent of the potassium, 70 per cent of the creatine, and 95 per cent of the acid-producing substances.[16] All of this is lost on the first day and therefore rapidly appears in these amounts in the urine; this means that the kidneys must excrete this large amount of material within an exceedingly short time. It is thought by many that this sudden loading of the kidneys with large amounts of probably toxic material for excretion may be responsible for the damage observed. These studies have been corroborated in experimental animals.

The Rôle of the Heme Derivatives. With destruction of muscle there is release of myoglobin.[10, 15, 16, 20, 25, 61, 73, 111] Hemoglobin is set free when

red cells are suddenly hemolyzed. When pigments are liberated in large quantities and cannot be metabolized in usual fashion by the liver to be excreted in the bile, they are excreted by the kidneys.[2, 8, 39, 60, 72, 78, 113] The mechanism by which the pigments reach the lumen of tubules is not clear. There are differences of opinion about the passage of hemoglobin molecules through the glomerular membranes. Since the molecular weight of hemoglobin is 68,000 and that of serum albumin is 70,000, it is considered by many observers to be unlikely that hemoglobin is able to pass through the glomerular membranes any more easily than serum albumin. However, several hypotheses have been presented to explain the mechanism by which hemoglobin enters the lumen of the nephron. One is that a small amount leaks through the glomeruli; a second is that some of the hemoglobin is broken into small components and is excreted as such; and a third is that damage to the tubules and glomeruli increases the permeability of these membranes to hemoglobin. None of these ideas is supported by sufficient direct data. As pointed out by Kreutzer and his associates,[57] who reviewed the data on the excretion of hemoglobin and myoglobin in the urine in a study of spontaneous myohemoglobinuria, little is known about the details.

Myoglobin has a molecular weight of 17,500, or is about one-fourth the size of the hemoglobin molecule, and it contains one iron atom instead of four. Because of the presence of iron, the benzidine or guaiac test for occult blood in the urine of patients with myoglobinuria is positive. The diagnosis of myohemoglobinuria should be considered if the urine is dark and yields a positive test for occult blood, is free from red cells, and if no evidences of hemolytic disease exist. Since a minimum of about 20 mg. of hemoglobin per 100 c.c. of plasma has to be reached in order to give a reddish tinge to the plasma and since myoglobin has a renal threshold of about 20 mg. per 100 c.c. whereas that of hemoglobin is 100 mg., the color of the plasma aids in differential diagnosis. Therefore, it is possible to rule out hemoglobinuria, if a sample taken just before the appearance of dark urine does not exhibit a reddish tinge. Of course, myoglobin can be differentiated from hemoglobin and identified easily by means of ultracentrifugation, ultrafiltration and by spectroscopic examination. Myoglobinuria might be confused with acute porphyrinuria, but this is relatively unlikely since the porphyrins do not give a positive reaction to the benzidine or guaiac tests for occult blood. However, such problems are not troublesome in the presence of the lower nephron syndrome, since the other phases of the disease are distinct. The small size of the myoglobin molecule, the low renal threshold, and the rapid liberation of myoglobin from damaged muscle all contribute to the sudden overloading of the kidneys whenever there is crushing or damage to large masses of muscle. Apparently the low renal threshold is related to the molecular size of 17,500, which is small enough to permit passage through an unaltered glomerular membrane.

The heme compounds are apparently concentrated or precipitated in the lower part of the nephron. This is true of that derived from hemoglobin

and probably of the myoglobin derivative as well. When it passes through the glomerular filter, a small portion is reabsorbed by the cells of the proximal tubules.[61] As a result there is a concentration of the material in the cells lining the tubules. Furthermore, as the pigment passes through the tubules, there is a tendency for it to be precipitated and accumulated within the lumen of these tubules.

Several hypotheses have been introduced to explain the process of the pigment precipitation. It is thought that the pigment is removed from solution, probably as hematin, when the intratubular fluid becomes sufficiently acid, that is, has a pH below 6, and when simultaneously water is reabsorbed and the material is concentrated. Such requirements are met in the lower nephron and collecting tubules. By means of intravenous injections of myoglobin Bywaters and Stead [21] were able to produce renal failure if the acidity of the urine reached levels of a pH of 4.5 to 6.1. They were unable, however, to repeat some of these experiments. It is because of the influence of low pH on the precipitation of these pigments that alkalinizing measures are employed therapeutically.

It is also believed that cellular injury is concerned with *precipitation* of these pigments in the tubules. Renal damage produced by ischemia results in the precipitation of the pigments in the tubules.

It is also stated that inadequate urinary flow through the tubules, effected by the decreased blood pressure and volume of glomerular filtration, and increased tubular reabsorption lead to accumulation and retention of the pigment in the lumina of the tubules. By dissection, however, Oliver [80] found many nephrons without casts. It is difficult to understand why certain nephrons show an accumulation of these casts and pigment whereas others do not.

It has not been demonstrated that *myoglobin or hemoglobin* is *toxic*. However, there may be some degradative products or derivatives which are. Some observers are of the opinion that such toxic substances exist and react more readily in an acid medium. There are no data available to demonstrate the existence of any toxic effects from these pigments. It has been proposed by several observers that the damage produced by these pigments is due to the *obstruction*, though Oliver's sections and dissections failed to reveal complete obstruction as far as the tubules were concerned. Many others have confirmed his observation. Furthermore, the nephron above the level of the casts fails to show any evidences of severe dilatation, as in hydronephrosis.

Other observers contend that a *toxic substance* might arise from injured tissue. This has been maintained to be true in the case of the crush syndrome, in which *toxins* are liberated in the area of muscular injury, in instances of burns, uteroplacental injury, and after administration of some drugs, such as sulfonamides and mercury. Proof is lacking that degradative products are liberated in ischemic muscles or burned areas which damage

the kidney. It has also been suggested that *organic* and *inorganic substances,* such as uric acid, phosphoric acid, potassium and creatine, liberated by injured tissue or toxic states, contribute to the renal damage.[9, 35, 50, 61, 64, 96]

Still others have suggested that *proteolytic enzymes* liberated in injured tissue may be responsible for the damage to the renal tubules.[76] Associated vomiting, disturbances in electrolyte balance, malnutrition, and dehydration may contribute to the intoxication and damage of the kidneys.[15, 16, 61] Disturbances in blood volume and in fluid balance could conceivably contribute to reduction in renal function, although such ideas remain conjectural.

It has also been proposed that disturbances in renal blood flow, particularly in the presence of shock, are of paramount importance in diminishing renal function and in damaging the nephron.[26, 32, 54, 59, 81, 88, 93, 98, 99, 102, 103] It has been observed that in patients suffering from shock, particularly if it is severe and prolonged, more severe damage to the tubules is sustained. This, however, may not be directly related to the shock, the latter being only another manifestation of the severity of the general injury. It is likely that all of the facts mentioned play some rôle, though the exact mechanism and the contributing rôle of each individual factor is not yet clear.

The mechanism by which oliguria develops is likewise unknown. Several hypotheses have been presented: (1) That it is due to a disturbance in glomerular filtration, which is the result of impairment of renal circulation.[4, 29, 37, 49, 53, 67, 71, 85, 91, 92, 95] This is related to the idea advanced by Trueta and his associates [100] of "shunting" of the renal circulation from the cortical portion of the kidneys to the medulla. It may be partially attributable to peripheral circulatory collapse and shock which impair glomerular filtration. (2) That oliguria results from tubular obstruction, which interferes with the rate of urinary flow. However, more and more observers are rejecting this concept. (3) That oliguria is incident to the disturbance in tubular reabsorption as a result of tubular damage from an impairment of renal circulation, a theory proposed by Phillips and coworkers [53, 85] and by others. The damaged areas, that is, the lower tubular portions of the nephron, become essentially parchment paper as far as selectivity of reabsorption is concerned.[15, 16, 53, 61, 85] Since there is no selective reabsorption, absorption of glomerular filtrate is complete qualitatively and almost quantitatively.[87] Consequently, the glomerular filtrate passes down the tubules and diffuses unaltered back into the circulation, so that there is almost complete reabsorption of the glomerular filtrate in its native state. This results in the formation of urine with approximately the same specific gravity as that of the glomerular filtrate, a value of 1.010. Lucké [61] and others are of the opinion that this almost complete leaking of glomerular filtrate through damaged tubular walls back into circulation is the best hypothesis to explain the histologic and clinical data of the lower nephron syndrome.

There are also many extrarenal factors concerned with the toxic picture. For example, anuria and azotemia will produce intoxication. Vomiting,

dehydration, hemorrhage, local injury, shock, and toxic materials, such as sulfonamides, mercury and products of infections, all make important contributions to the general clinical picture observed in the syndrome.

The Urine and the Renal Function

After crushing injury, the first urine is usually acid and is brown because of the pigment of acid hematin.[15, 16, 61, 74] The mistaken idea that this indicates the presence of erythrocytes is disproved by microscopic examination. The supernatant urine may be normal in color but is usually smoky. If the pH approaches neutrality, the urine tends to be red with little or no sediment. The first urine passed after injury is rarely normal because, as mentioned previously, the release and excretion of myoglobin or hemoglobin is extremely rapid. When the systolic blood pressure drops below 70 or 80 mm. of mercury, little urine is excreted.

The pigment in the urine usually shows a broad band in the red zone, signifying a metmyoglobin compound, as well as two bands in the yellow-green portion, which closely resemble those of oxyhemoglobin. Excretion of pigment begins to decrease in one to two days, and casts start to appear in the urine in large quantities. At first, they are pigmented casts or aggregations of pigmentary granules formed in the casts; these become stringy, and at the end of the first week the pigment core is covered by layers of desquamating epithelial cells. Occasionally the casts found later in the disease may be entirely cellular. It is at this time, as indicated in the discussion on pathology, that cellular desquamation and new growth reach their maxima. The amount of urine excreted decreases progressively and during the first week may reach values of 25 to 50 c.c. in 24 hours. The composition of the urine resembles that of glomerular filtrate. The concentration of urea is low, often less than 1 gm. per 100 c.c., whereas the blood urea may be as high as 300 mg. per c.c. Chloride concentration tends to be high in the urine despite lower than normal blood concentration. Reducing substances are occasionally found in small amounts, and potassium and creatine are present in abnormally large quantities. This, of course, is particularly true when the crushing syndrome causes extensive muscular damage.

Nitrogen retention is associated with the decrease in renal function. The patient begins to exhibit drowsiness with the development of uremia. As stated previously, the blood chloride level tends to fall, and the carbon dioxide combining power declines, due to liberation of lactic acid and other inorganic acids from the damaged tissue and loss of normal acid base regulatory function of the kidneys.

There have been a number of studies recently on the effect of hemorrhage, shock and crushing injury on renal function. Van Slyke and his associates,[102] for example, found that hemorrhage produced experimentally in dogs causes severe vasoconstriction associated with the drop in blood volume. This maintains glomerular filtration, provided that the vasocon-

striction does not selectively involve the cortical portions of the kidney. When shock progresses so that the blood pressure reaches extremely low values, the filtration pressure is decreased and the quantity of glomerular filtrate becomes reduced. Corcoran, Taylor and Page [26] found a decrease in renal blood flow due almost entirely to an increase in renal vascular resistance in dogs following release of the tourniquets in "tourniquet-produced" shock. This is brought about by the increase in blood viscosity and by vasoconstriction of the afferent and efferent glomerular arterioles. Pain is of little influence, as blocking of sympathetic nerves has no effect upon renal function. Apparently, therefore, vasoconstriction is humoral in origin.

Phillips and his associates [53, 85] have shown that ischemia produced by gently clamping the renal arteries will interfere especially with tubular function. The main effect is to decrease selective absorption of the tubules so that glomerular filtrate is absorbed almost completely, the tubules becoming essentially parchment membranes, instead of living membranes with ability to absorb selectively. Similar observations have been made by Badenoch and Darmady.[4] These latter authors were able to produce disturbances in the distal segments, including patchy necrosis similar to that described by Bywaters [15] and Lucké.[61] Apparently, there was correlation between the histologic picture and disturbances in renal function.

Sequelae. The fatality rate is extremely high, the survival rate varying between 10 and 33 per cent. As far as is known, those who survive apparently do not experience residual disturbances in renal function, although it is not clear from published reports whether or not adequate follow-up studies have been conducted. A prolonged follow-up period would be required to ascertain the residual renal state. It is well to bear in mind when estimating morbidity that patients with the most severe damage die whereas those with the least survive; therefore, a follow-up of renal function would necessarily include only those with mild damage. With improvement in therapeutic methods, increased survival rate of the more seriously ill patient will result, thus permitting better evaluation of the problem of morbidity, particularly if follow-up studies are emphasized.

Treatment

Before a discussion is undertaken of the management of the patient in whom the syndrome has developed, it is necessary to point out that there are certain types of the lower nephron syndrome which can be readily prevented. Most transfusion reactions are avoidable, being due entirely to carelessness. The same is true of intoxications, especially sulfonamides; more care in the selection of patients and during administration should reduce the incidence of injury from sulfonamides. Furthermore, when the slightest evidence of damage appears, immediate discontinuance of these drugs will usually result in minimal injury. It is the neglected patients who sustain the greatest damage. Uteroplacental damage with the complicating lower nephron syn-

drome has been reduced by more adequate care of the problems of pregnancy and the control of criminal abortion. The same is true for accidents and burns as well as the control of intoxications from mercury. A study of the incidence of the lower nephron syndrome reveals that most cases encountered in civilian practice are preventable and are usually the result of negligence.

Once the patient has had an injury or a reaction which is known to produce lower nephron nephrosis, steps should be taken immediately to *prevent* its development. These measures are based in part upon physiologic phenomena concerned with sudden liberation of myoglobin or hemoglobin in the plasma and consist in immediate hospitalization of the patient, with careful attention and nursing. Fluids should be administered in quantities sufficient to maintain diuresis. Alkali, such as sodium bicarbonate, should be given to maintain an alkaline urine, determined not by an arbitrary dose but by the simple expedient of red litmus dropped into the urine. These patients should be carefully watched so that oliguria may be noted immediately, since the administration of alkali and fluids is governed by the output. Overloading with fluid is dangerous [97] and may lead to pulmonary edema. Intake and output of fluid should be charted carefully. The patient should be examined frequently for evidences of edema, and the changes in blood chemical values should be followed closely. Patients such as those who have had severe burns or those who have been severely injured by compression must be under close observation for the possibility of shock. Should it develop, the usual therapeutic measures should be employed, including the use of either whole blood or plasma. It is stated that loss of great quantities of fluid into large masses of injured tissues may result in oligemic shock. Blood volume must therefore be maintained, but therapy must be based upon objective data, derived from the usual laboratory procedures, including hematocrit, blood count, and blood protein and serum chloride determinations. Such studies may permit early recognition of shock or predisposition to it. The blood pressure, of course, should be recorded at frequent intervals. If hemorrhage occurs, it is necessary to replace the lost blood.

Morphine should be given for pain and the patient should be made comfortably warm but should not be overheated. Local surgical treatment of the injured areas should be given adequate attention. It has been suggested that the parts should be immobilized and the limb cooled with icebags in order to decrease the rate of autolysis and absorption of toxic materials. This cooling process has been reported to be successful in the hands of some but not all. If there is considerable pressure in the region of large vessels and it is thought that this tension is resulting in obstruction, splitting of fascia by means of incisions made along the course of the vessels of the limbs has been recommended but is not generally advocated. Casts, if employed, should be applied carefully and observed closely, since constriction resulting from development of edema with increase in volume of the part may result in further arterial obstruction. Obviously, it is important to avoid constricting bandages.[16]

The rôle of sympathetic blocking or sympathectomy is yet to be evaluated. Amputation should be performed if the part is definitely useless but unless it is done within the first 24 hours, postponement may be necessary, particularly if renal damage is serious.[16] Under such conditions, splinting and physical therapy should be employed until amputation can be performed.

Once renal failure, with oliguria and progressive uremia, develops, relatively little can be done except for the use of some of the more experimental procedures now under investigation, such as the artificial kidney or dialysis. It has been suggested that fluids should be administered to these patients in the presence of anuria and oliguria. However, it is well to remember that large quantities of fluids may produce severe edema and increase the damage. Sodium lactate, 5 per cent glucose, and sodium chloride may be used in amounts governed as much as possible by studies of the blood chemistry and by the clinical state. Human Ringer's solution may also be used. It is possible to administer fluids by means of gastric or duodenal tubes if the patient is not vomiting excessively; otherwise, intravenous medication must be employed. Fluids should not be administered to any extent beyond that which produces slight edema; in these amounts fluids might dilute the toxins and at the same time produce diuresis once renal function begins. Mercurial diuretics and decapsulation have been advocated, but it is unlikely that the latter is of any value. If results are not obtained promptly with mercurial diuretics, they should be discontinued. However, in view of the nature of the lesions and the mechanism of action of mercurials, it is likewise unlikely that these would be of great value—in fact, actual increased damage might result. One or two doses will probably be accompanied by no deleterious effects.

The Artificial Kidney. There has been increased interest in the use of artificial methods for eliminating metabolites. These procedures are based upon the principle that a method, even if crude, which would eliminate toxic substances during acute renal failure might prolong life long enough to permit renal repair and return of renal function. This idea is not a new one; it was advocated as early as 1923.[44, 52, 79] A number of papers have been published suggesting this procedure or peritoneal lavage: that of Ganter [44] in 1923, Landsberg and Gnoinski [58] in 1925, Rosenak and Siwon [90] in 1926, Bliss, Kastler and Nadler [11] in 1932, Haam and Fine [51] in 1932, Rhoads [86] in 1938, Balazs and his associates [6] in 1934, Wear, Sisk and Trinkle [106] in 1938, Fine, Frank and Seligman [40] in 1946, Buckley and Scholten [13] in 1947, and Basset and coworkers [7] in 1947.

The method of peritoneal lavage consists in placing a catheter in an upper lateral abdominal quadrant and another in the lower contralateral abdominal quadrant and running a large quantity of a modified Tyrode's solution through the peritoneal cavity. This is done continuously, 18 to 24 liters being used in 24 or 48 hours. The formulae for these solutions may be found in the aforementioned papers describing the technic. These solutions have sulfadiazine, heparin, and penicillin added in order to prevent

clotting and infection. When the physician is interested in removing fluid from the body, the solution is made slightly hypertonic by increasing the amount of glucose, and when it is desired to administer fluid through the peritoneum, the solution is made hypotonic by decreasing the concentration of the glucose. Fibrin usually forms in sufficiently large quantities to obstruct the flow of the fluid. Disturbances in bowel function, such as ileus, nausea, vomiting and abdominal distention and pain, frequently develop. Peritoneal lavage is not a satisfactory procedure; most patients treated by this method have died.

Another method consists in the use of the *artificial kidney*. Circulating substances in the blood which are diffusable are removed by dialysis through a dialyzing membrane.[1, 52, 78, 79] Probably the first paper suggesting this method is that of Abel, Rowntree and Turner,[1] published in 1914; they studied dogs and suggested that the same procedure might be applied to man. Their apparatus consisted of many dichotomously branching dialyzing tubes submerged in a dialyzing fluid. After a period of dialysis the blood is returned to the animal. Kolff [56] in 1944, described an artificial kidney which consisted of a large drum upon which 40 to 45 yards of visking cellulose tubing were wound in spiral fashion. The drum rotates, passing the cellulose tubing through a tray of dialyzing fluid. Blood from the patient enters from an artery into one end of the tubing and is returned to a vein from the other end. By means of gravity, the blood is made to progress down this spiral tube for dialysis. More recently others have begun to modify Kolff's technic. A few patients have been saved by means of this artificial kidney. As much as 120 liters of blood have been made to flow through the artificial kidney. One or several treatments may be given, depending upon the condition of the patient and the success of each treatment. As much as 263 gm. of urea have been removed, and in one patient, for example, blood urea declined from 704 to 192 mg. per 100 c.c. Usually if dialysis is attempted for the second time and results are not satisfactory, it is not repeated. Kolff and his associates are still studying this problem.

More recently, *gastric lavage* has been advocated during the period of oliguria to eliminate retained products of metabolism. The paper of Vermooten and Hare [104] suggested gastric lavage with the use of a special gastric tube, preferably with two lumina, a duplex afferent and efferent tube. Two separate tubes are less satisfactory, since it is not possible to be certain of the relative positions of the openings of the separate afferent and efferent tubes. The method of gastric lavage consists in continuously irrigating the stomach with about 10 liters of a special irrigating fluid over a period of 24 hours. The rate of irrigation is about 150 drops per minute. These authors have been able to remove some urea by this technic. It was not possible to evaluate properly the precise effect of the procedure in their patient. However, it is a procedure which deserves further investigation.

Rogers, Sellers and Gornall [89] suggested the use of *intestinal irrigation* in the treatment of acute uremia, oliguria or anuria. These authors used a

triple-bore, thin-walled rubber tube with a small balloon at its tip. In experimental animals, the tube was passed various distances down the intestinal tract, the balloon was inflated and the intestinal tract was irrigated with the perfusion fluid. Warm physiologic saline solution was used. The observers were able to reduce azotemia from 198 to 126, from 198 to 112, from 231 to 145 mg. per 100 c.c. in separate animals, using 12 to 18 liters of fluid over a period of about six hours. They found that the return rinsing fluid contained from 4.3 to 5.4 gm. of nonprotein nitrogen. This idea is essentially the same as gastric lavage but should be more promising because of the more rapid diffusion of materials and greater diffusion areas. Further investigations are definitely indicated.

As indicated by all investigators, if the patient survives the period of acute uremia and the acute disease so that repair may take place, diuresis would be established in many severely injured patients. The percentage of patients who sustain serious damage and who will again produce urine is undetermined. There must be some limit to the degree of damage and the ability for repair. Postmortem studies have indicated that if some of the patients had been able to survive a few more days, it is likely that renal function would have returned to normal. The therapeutic problem is to prolong life during a brief critical period. General hospitals with proper laboratory facilities and trained personnel should be prepared to employ the new procedures previously described, which promise to be life saving.

General Therapeutic Measures. It is important to remember that certain general measures must be emphasized in the management of these patients. Most important of all is *good nursing.* The patient should have constant attention, particularly when he is having his greatest difficulty. He should be made mentally as well as physically comfortable, since he is apt to become apprehensive and anxious about his disease. Most patients know they are seriously ill and are aware of the fact that they are likely to die.

Attention to electrolyte balance, fluids, vitamins, and nutrition should be emphasized. If possible, a large portion of the necessary fluids and carbohydrates should be given by gastric or duodenal tube. Protein intake should be held to a minimum during the time of renal failure, for the metabolism of administered proteins will only increase the rate of accumulation of nonprotein nitrogen and toxic protein substances.

Borst [12] has found that a diet low or absent in protein, consisting almost entirely of fat and carbohydrate, is of considerable value in the management of acute renal insufficiency. Some of his patients were fed a diet consisting of 150 gm. of butter and 200 gm. of sugar, a total of 2,000 calories. This yields practically no protein and little potassium and phosphorus. Patients have received this diet for over three consecutive weeks, except for variations in quantity, without difficulty and with great benefit during periods of uremia. Contrary to most opinions, severe-to-complete restriction of proteins in the diet reduces protein catabolism to extremely low levels, so that by the end of three days the daily nitrogen excretion is less than 6 gm., and

less than 4 gm. daily by the end of 14 days. By the end of three days the potassium excretion is about 30 mEq. per day and 10 mEq. by the end of 14 days. Another diet prepared by Borst, a gruel consisting of 1.5 liters of water, 100 gm. of custard powder, 150 gm. of sugar and 100 gm. of butter and providing 1,750 calories, has been found useful in the cases under discussion.

During the period of recovery, the food intake should be calculated so as not to overburden the kidneys until they have made complete recovery. Proteins, particularly animal proteins, must not be administered in large quantities. To evaluate the completeness of recovery, repeated studies of renal function, including Addis counts, should be made. Defects in renal function may persist for many months, if not permanently, and may require appropriate regulation of the patient's regime.

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NECROSIS OF RENAL PAPILLAE *

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Introduction

Necrosis of the renal papillae is a curious and striking lesion which most pathologists meet only occasionally at the autopsy table. The purpose of this presentation is to report briefly the cases of this disease seen at the Queens General Hospital, to discuss some of the theories of its pathogenesis, and more particularly, to relate this lesion to a similar one produced in the experimental animal by a dietary deficiency of certain fatty acids.

Necrosis of Renal Papillae in Man. The literature concerning this lesion, which is variously known as renal papillitis, medullary necrosis, papillitis necroticans, necrotizing renal papillitis, etc. has recently been reviewed in detail by Edmondson, Martin, and Evans.[1] These authors have traced the first case report back to 1877, but Günther [2] in 1937 first emphasized the frequent association of diabetes with this lesion.

Approximately 110 cases were reported in the literature up to 1947,[1, 4, 5] and of these, 62 had diabetes and 48 did not; of the latter, 85 per cent had urinary tract obstruction. From the large series reported by Edmondson et al.[1] and by Robbins, S. L., Mallory and Kinney,[5] it is apparent that 12 to 20 per cent of diabetics coming to autopsy have acute pyelonephritis. Of these, 25 per cent have necrosis of the papillae. Hence the lesion may be found in 3.2 to 5 per cent of all diabetics. In contrast, 3.3 per cent of non-diabetics coming to autopsy have acute pyelonephritis. Of these, 2 per cent have necrosis of the papillae. Hence the lesion may be found in only 0.06 per cent of non-diabetics. The overall incidence of the disease in pyelonephritis is about 4 per cent.[1] Robbins, Mallory and Kinney found that in 74 per cent of their cases, death was attributable directly to the papillary necrosis.

The great majority of non-diabetics who have papillary necrosis have some obstruction of the urinary tract. This was present in six out of seven cases in one series,[5] in 20 out of 21 cases [1] in another; and in five out of six of our cases. Benign hypertrophy of the prostate is the usual cause, but carcinoma of the prostate, urethral stricture, "cord" bladder and renal calculi have also been found.

The variation in sex incidence is also striking. In diabetics, the ratio of females to males is 2:1; in non-diabetics the ratio of females to males is 1:6, due to greater frequency of urinary tract obstruction in males, chiefly

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from the prostate. The clinical picture of this disease may be acute or subacute. The acute cases are usually diabetics who have a short history of illness, often with a sudden onset, with a rapidly fatal course over a period of a few days. They are often seen in coma, with or without acidosis, and usually have azotemia. There is pyuria, often hematuria, a high fever and often leukocytosis. The subacute cases, usually, are: (1) diabetics with pyelonephritis that have been followed for a period of days or weeks, who suddenly became worse; (2) diabetics who develop a septicemia secondary to some focus of infection, e.g., a carbuncle, and are found to have pyuria and azotemia,[1] (3) non-diabetics, usually with chronic obstruction of the urinary tract, who develop a severe urinary tract infection, with sepsis and azotemia. The course of the latter group is difficult to differentiate from suppurative pyelonephritis without papillary necrosis.

Occasionally the sloughing of a papilla will result in renal colic, and/or hematuria, with a defect of the calyces on pyelography, which may suggest renal stone, tumor, or tuberculosis.[2] Alken [3] described a case of a female diabetic with pyuria and hematuria, with defects in some calyces on pyelography. Six months later a sloughed papilla was passed, and pyelography demonstrated defects in all the calyces.

The kidneys are usually enlarged and heavier than normal. The cortex is usually studded with abscesses. The papillary necrosis is bilateral in the majority of diabetics, but more often unilateral in the majority of non-diabetics. The degree of necrosis of the renal papilla varies. It may be (1) confined to the tip of the papilla, (2) confined to a small central portion of the papilla, (3) involve most of the papilla, (4) involve all of the papilla and part of the pyramid (extending in rare cases up to the corticomedullary junction), (5) the necrotic papilla may show a separation at the line of demarcation from the rest of the pyramid, (6) the papilla may be sloughed out entirely. The renal columns of Bertini are never involved, nor does the lesion ever extend to involve the cortex. The necrotic papillae are brownish, or yellowish-green in color and are sharply demarcated from the rest of the kidney.

Microscopically there is an acute pyelonephritis with or without suppuration in the cortex and medulla. The affected papillae show a pale staining, infarct-like necrosis of all elements—tubules and interstitial tissue, with shadow-form preservation of the general architecture. In the collecting tubules, there may be found bluish masses of cocci or rod-shaped bacteria; but in the necrotic papilla there are no interstitial abscesses or diffuse inflammatory infiltrate. At the line of demarcation, there is a zone of infiltration of polymorphonuclears and round cells, along a narrow line of necrotic tissue, and above this, marked vascular congestion. An acute pyelitis of varying severity is present.

Necrosis of Renal Papillae in a Deficiency Disease of Rats. In 1929 Burr and Burr [7] described a new deficiency disease in rats fed a diet which

was virtually fat-free. This diet consisted of sucrose, casein which was carefully purified and rendered fat free by ether extraction, McCallum's salt mixture, ether extracted yeast for the vitamin B complex, the non-saponifiable matter from cod liver oil for vitamins A and D, and in later experiments the non-saponifiable matter from wheat germ oil for vitamin E.

Rats fed such a diet from the day of weaning develop (1) a lesion of the tail characterized by scaliness, inflammation, swelling, and later necrosis of the tip, (2) redness, swelling and scaliness of the feet, (3) dandruff and loss of body hair, (4) cessation of growth, (5) bloody urine. The animals maintained a plateau of the weight curve for weeks and months, then declined in weight and died. At autopsy, five of the eight animals had abnormal kidneys. It was felt that the immediate cause of death was kidney degeneration.

The addition of 10 drops of lard daily to the diet of these diseased animals produced a prompt cure of all lesions and a gain in weight; while the addition of 2 per cent of the total diet as lard from the beginning of the experiment completely protected the animal from the disease. Furthermore, the addition of pure glycerol, or the non-saponifiable matter from lard did not protect against the disease, but 13 drops of the fatty acid fraction from lard did give protection. Feeding 200 mg. per day of the fatty acid fraction of lard to a diseased rat on the fat free diet produced a 2 gram/day increase in weight, a tenfold effect.

They demonstrated by a series of experiments that (1) the disease is not due to a deficiency of vitamins A, B, D or E; (2) the fat free yeast, and the non-saponifiable matter from cod liver oil, and from wheat germ oil, were adequate sources of these vitamins and that (3) these latter substances were absorbed in the absence of fat in the diet. By feeding oils of various composition with regard to saturated and unsaturated fatty acids, it was shown that cures could only be effected by unsaturated fatty acids, and of these, only linoleic or acids of higher unsaturation. Oleic acid, and saturated fatty acids were without effect. The authors concluded that warm blooded animals cannot synthesize appreciable quantities of linoleic acid, or more unsaturated fatty acids.

Later experiments [8] demonstrated that (1) the respiratory quotient of rats with the fat deficiency disease rises above unity after carbohydrate feeding, indicating the formation of fat from carbohydrate, but the persistence of the disease proves that linoleic or other more unsaturated fatty acids are not formed.[9] (2) The highly unsaturated fatty acids of cod liver oil can be used by fat deficient rats for growth, but the skin lesions can only be cured by linoleic or linolenic acids, which are lacking in cod liver oil.[10] (3) Feeding pure fatty acids as the methyl esters proves again the complete ineffectiveness of oleic acid, the curative value of linoleic and linolenic acids, and the ineffectiveness of alpha eleostearic acid, an isomer of linolenic acid.[11] (4) The scaly skin and tail necrosis in this disease are not a symptom com-

plex unique to fat deficiency but are found in other deficiency states as in malnutrition, avitaminosis B, avitaminosis G, diets containing rancid fat, and those rich in egg white. However, these changes, plus growth arrest and kidney degeneration (in the presence of adequate quantities of water soluble growth factors, together with vitamins A, D, and E), which are readily cured by an adequate fat, constitute a specific disease complex.[12] (5) The iodine number of serum fatty acids of rats on fat free diet indicates that these fatty acids are less unsaturated than controls.[13, 14] (6) Metabolism studies on fat deficient rats indicate that the basal metabolic rate is higher, the respiratory quotient higher, and the specific dynamic action of foods is higher, and that these rats synthesize large amounts of fat but this does not prevent their fat deficiency syndrome.[15] (7) Feeding pure fatty acids to fat deficient rats discloses certain differences in the effects produced by linoleic, linolenic and arachidonic acids, and hence they must be treated individually in nutrition studies.[16]

In 1931, Borland and Jackson [17] reported the pathology of the kidneys of rats fed on the fat free diet of Burr and Burr. The results were as follows: A group of 21 rats with the fat deficiency disease were autopsied. The kidneys were large and pale, with an average weight of 21 per cent over the Wistar norm. Some were coarsely granular. In eight of the 21 animals, the papillae appeared largely necrotic and much of certain papillae might be sloughed off into the pelvis. In these, irregular masses of the necrotic material stained a deep blue with hematoxylin and black with von Kossa's stain, demonstrating calcium.

Microscopy revealed no changes in the glomeruli. Certain cortical tubules showed cells which stained deep blue with hematoxylin, and black with von Kossa's stain, indicating the deposition of calcium. The lumina of these tubules often contained debris which was also calcified. These changes were present in 15 of the 21 cases. There was no inflammatory infiltrate noted. Widespread degenerative changes in cortical tubules (sloughing of cytoplasm, pyknosis, etc.) occurred in eight cases. Sudan III stains showed increase in intracellular fat or lipoid in 18 cases. Occasionally there was dilatation of some of the cortical tubules, suggesting obstruction to the flow of urine in the papillary ducts. In the medulla, degenerative changes were found in cells of the papillary ducts. Sudan III stains showed fine fat or lipoid droplets in these cells and adjacent interstitial tissue. Fatty casts and casts of a homogenous blue-staining substance were often present. Higher up in the pyramid, casts of fatty albuminous material appeared in degenerating ducts, and, as the necrotic area was approached, this material as well as the degenerating tissue became intermingled with deposits of calcium. In two of these eight cases, bacteria and a few polymorphonuclear leukocytes were present in the necrotic area, but in the remaining kidneys no inflammation was found.

In 10 cases, proliferation of the pelvic epithelium occurred, but no keratosis such as is found in avitaminosis A was present. In a group of rats

with fat deficiency disease, in which cures were attempted with various inadequate fats, the same changes were noted as above. However, calcification of the papilla and apical necrosis were present in one rat of nine. In a group of rats in whom the deficiency disease was first induced, and then cured by the addition of lard to the diet, the kidneys were normal grossly and microscopically. Another group of 35 rats with the fat deficiency disease was treated with various fats including linseed oil, corn oil, olive oil, etc. At autopsy, the general condition was fair to good, the animals being only 10 per cent underweight on an average. However, degenerative changes and calcification of cortical tubule cells were widespread. Degeneration of papillary ducts was found in 21 cases, with calcification and necrosis of the papillae in seven of the 21. The necrotic areas were smaller than those found in the first group.

Thirty-eight rats, which were fed diets containing lard, or a regular stock diet, were used as the controls.

These authors concluded that characteristic renal lesions were present in rats fed on a diet free of fat but otherwise adequate. The most striking lesion was calcification of tubules and necrotic areas in the renal medulla, with disintegration of the apex of the pyramid in some. The addition of lard to the diet prevented the renal lesion, or cured it to a large extent.

Material

Fourteen cases of papillary necrosis which were autopsied at the Queens General Hospital, are described below. These include 13 acute cases, and one which was healed. Eight of these cases were diabetics and six non-diabetics.

Diabetic Cases

Seven acute cases, and one with healed papillitis were found in diabetics. (The latter will be discussed separately.) There were six females, and two males, in an age range from 42 to 79 years, with an average age of 57. Two patients were admitted to the hospital in coma, and one was stuporous. Three patients died in 18 hours or less after entering the hospital. Two of these had 3 to 4 plus glycosuria, but no acetone; yet both were thought to be in diabetic coma. The shortest total duration of illness from the first symptoms was 3.5 days. The urine was abnormal in all the acute cases, though only three were noted to have pyuria. In the three acute cases in which blood urea levels were done, all had marked azotemia. In the four cases in which the hemoglobin was reported, it varied from 8.5 to 10.5 grams, with red cell counts between 3 and 3.5 million. Three had unilateral papillary necrosis, and two showed unilateral pyelonephritis.

The single male patient in the acute cases had benign prostatic hypertrophy with urinary retention and a cystotomy was performed during his hospital course.

Case Reports

Case 1. This 42 year old white female was admitted to the hospital in coma. She was known to have had diabetes for 12 years. For the past week, she had been semi-comatose.

Physical examination revealed an emaciated woman in deep coma, with twitching of the facial muscles, and a uremic frost on the skin. Blood pressure 118 mm. Hg

Fig. 1. Kidney of a diabetic patient showing extensive suppurative pyelonephritis with sharply limited zones of necrosis in the pyramids. Note the narrow hyperemic and exudative marginal reactive zones.

systolic and 58 mm. diastolic; temperature 101.2°; respirations rapid. Laboratory data: Urine: grossly bloody; sugar 3 plus; acetone 0; albumin 3 plus; many casts.

The patient made no response to treatment (insulin and infusions) and died 18 hours after admission.

Clinical diagnosis: Uremia; diabetic coma; malnutrition and avitaminosis.

At autopsy, the kidneys contained multiple cortical abscesses, with a perirenal abscess on the left. Necrosis of the papillae was present in the left kidney. The pelves and ureters were dilated and revealed ecchymoses. There was a bullous hemorrhagic cystitis. Microscopy revealed advanced papillary necrosis (figures 1 and 2).

Case 2. This 57 year old Negro female was admitted in coma. The past history was not known, but she was reported to have been "sick" for eight days. On physi-

FIG. 2. Micro-photograph showing junction zones between necrotic tissue of papilla and viable tissue with inflammatory reaction in between.

cal examination, she was in deep coma, dehydrated, hyperpneic, and had an acetone odor on the breath. Temperature 102°.

Laboratory data: Urine: milky; glucose 4 plus, acetone 3 plus; loaded with pus cells and pus casts. Six hours later, after she had received 725 units of insulin, three liters of Hartman's solution, and intravenous sulfadiazine, the glycosuria fell to 1 plus, the acetonuria disappeared, and she showed signs of returning consciousness. She

died suddenly, 11 hours after admission. An ante-mortem blood culture grew *B. coli.*

Clinical diagnosis: diabetic coma; pyelonephritis; *B. coli* septicemia.

At autopsy, the right kidney contained many cortical and medullary abscesses. The right ureter was dilated and had a thickened wall. The left kidney and ureter were unremarkable. The bladder had a hemorrhagic mucosa. Papillary necrosis was found and very marked on microscopic section.

Case 3. A 49 year old white female was admitted with a three day history of abdominal pain, nausea and vomiting. She was known to have diabetes for 12 years. She had not eaten nor taken insulin for the past three days.

Physical examination revealed an obese patient, with temperature 99.6°, and blood pressure 114 mm. Hg systolic and 76 mm. diastolic. The heart was not enlarged. The knee jerks and ankle jerks were absent.

Laboratory data: Initial urine: albumin, trace; glucose 4 plus; acetone 0; microscopically negative. Blood urea 52 mg. per cent, creatinine 3 mg. per cent, sugar 400 mg. per cent. White blood cells 7500, 83 per cent polys, later 19,100; Hb. 8.5 gm.

Four days after admission the patient suddenly went into shock, with pale, clammy skin, low blood pressure, and cyanosis. Complete heart block was noted. She died on the seventh hospital day.

Clinical diagnosis: Arteriosclerotic heart disease with myocardial infarction; diabetes mellitus with neuropathy.

At autopsy, the left kidney contained many cortical abscesses, and areas of "pallor" in the pyramids. The left pelvis and ureter were dilated and hemorrhagic. The right kidney, pelvis, and ureter were unremarkable. The bladder mucosa was thickened and red about the left ureteral orifice. The microscopic examination revealed advanced papillary necrosis.

Case 4. This 63 year old white male entered the hospital with a four year history of urinary frequency, nocturia, urgency and dribbling. For the past three days he had been vomiting and complained of an acid taste in the mouth. He was known to have diabetes for many years but was controlled without insulin.

Physical examination revealed 2 plus enlargement of the prostate which was soft and not fixed. Blood pressure 150 mm. Hg systolic and 80 mm. diastolic. He had uncontrollable hiccoughing.

Laboratory data: Urine: glucose 4 plus; 15 white cells per high power field. White blood cells 16,200; 87 per cent polynuclears; Hb. 8.5; red blood cells 3.4 million. Blood urea 65 mg. per cent; blood sugar 416 mg. per cent.

He was given insulin, penicillin, sulfa drug and infusion. The blood urea returned to normal in 11 days. The blood sugar dropped to 250 mg. He began to run an irregular fever up to 102°. A cystotomy was performed. The urea then rose to 41. CO_2 combining power was reported as 41 vol. per cent.

Bladder culture grew *Streptococcus hemolyticus* and *B. proteus.* He grew weaker, developed bed sores, and died on the twenty-eighth hospital day.

Clinical diagnosis: Pyelonephritis; diabetes mellitus.

At autopsy, the kidneys contained multiple cortical abscesses, the pelves were dilated and had red granular mucosa. There was an acute ureteritis and cystitis. Microscopic sections disclosed circumscribed areas of shadow necrosis within the papillae.

Case 5. This 73 year old, white female entered the hospital because of a sore on the big toe which had been present for several months. She was known to have had diabetes for six years.

Physical examination: There was gangrene of the big toe. Blood pressure 130 mm. Hg systolic and 76 mm. diastolic.

Laboratory data: Urine: Albumin 3 plus; glucose 2 plus; microscopically negative; Hb. 9.5 gm.; red blood cells 3.29 millions; white blood cells 7650. Blood sugar 315 mg. per cent.

She developed an abscess of the buttock, which was incised and drained. She ran a spiking temperature, deteriorated rapidly, and died on the eleventh post operative day (the fifty-first hospital day).

Clinical diagnosis: Diabetes mellitus; arteriosclerotic heart disease; abscess of buttocks; bronchopneumonia.

At autopsy, the kidneys were large, pale, and contained many cortical abscesses. There was bilateral renal papillitis, bilateral ureteritis, and cystitis. Microscopy showed circumscribed areas of typical necrosis of the renal papillae.

Case 6. This 43 year old, white female had fractured the right hip 10 weeks previously. After three weeks at another hospital, she was sent home where she began to vomit continuously for the next two weeks. For the past 12 days the urine had been bloody, and there had been a bloody stool on the day of admission. The past history included treatment for lues and known diabetes for 14 years.

Physical examination revealed a stuporous pale patient, with Argyll-Robertson pupils, absent knee and ankle jerks; and blood pressure 80 mm. Hg systolic and 60 mm. diastolic.

Laboratory data: Urine—albumin 2 +, glucose 0, acetone 0, micro-clumps of pus cells and many red blood cells. Hemoglobin 8 gm., white blood cells 15,200 with 88 per cent polynuclears. Blood urea 170 mg. per cent. Blood sugar 140 mg. per cent.

Cystoscopy revealed a necrotizing cystitis with involvement of the trigone. The blood urea fell to 85 mg. per cent but CO_2 combining power was found to be 33 vol. per cent. Culture of the bladder: *B. coli* and *Streptococcus non-hemolyticus*. The white blood count rose to 30,700 with 89 per cent polynuclears. The urines were maintained sugar free. She died on the tenth hospital day.

Clinical Diagnosis: Diabetes mellitus; necrotizing cystitis; acute pyelonephritis.

At autopsy the kidneys were large and smooth. All the renal papillae showed yellowish necrosis. There was an acute ureteritis and a severe hemorrhagic cystitis. Microscopy revealed an advanced papillary necrosis.

Case 7. This 52 year old white female was admitted with a six hour history of aphasia and weakness of the legs. She had complained of being "sick" for the previous three days but the nature of her complaints was not known. She had complained of headaches, dizziness and nocturia for the past year.

Physical examination revealed an obese, aphasic patient with a temperature of 99.2°. There was no paralysis of the extremities, but the left naso-labial fold was flattened. The plantar reflexes were normal.

Laboratory data: Urine—glucose 4 plus, acetone 0, no casts, microscopically negative.

Her temperature rose rapidly to 105.4°. She died 17 hours after admission.

Clinical diagnosis: Cerebrovascular accident; diabetes mellitus.

At autopsy the papillae of both kidneys were necrotic. The pelves were injected; the ureters and bladder were unremarkable. There were no areas of hemorrhage or softening in the brain. On microscopy the necrosis of the papillae was advanced.

Case 8. This 79 year old white male was admitted from a convalescent home. One month previously his right leg had been amputated for gangrene. He was a known diabetic, regulated by diet alone. On admission he was pale and disoriented. The blood pressure was 130 mm. Hg systolic and 80 mm. diastolic. The heart was enlarged. Basal râles were present in both lungs. The prostate was 3 plus enlarged, hard, nodular and non-tender. There was a right mid-thigh amputation stump.

Laboratory data: Urine—albumin 0, sugar 0, white blood cells 8000, hemoglobin 8 gm. Blood urea 17 mg. per cent, blood sugar 98 mg. per cent. A chest roentgen-ray was reported as negative.

He was treated with mercupurin and digitalis. A low grade fever appeared. Death occurred on the eleventh hospital day.

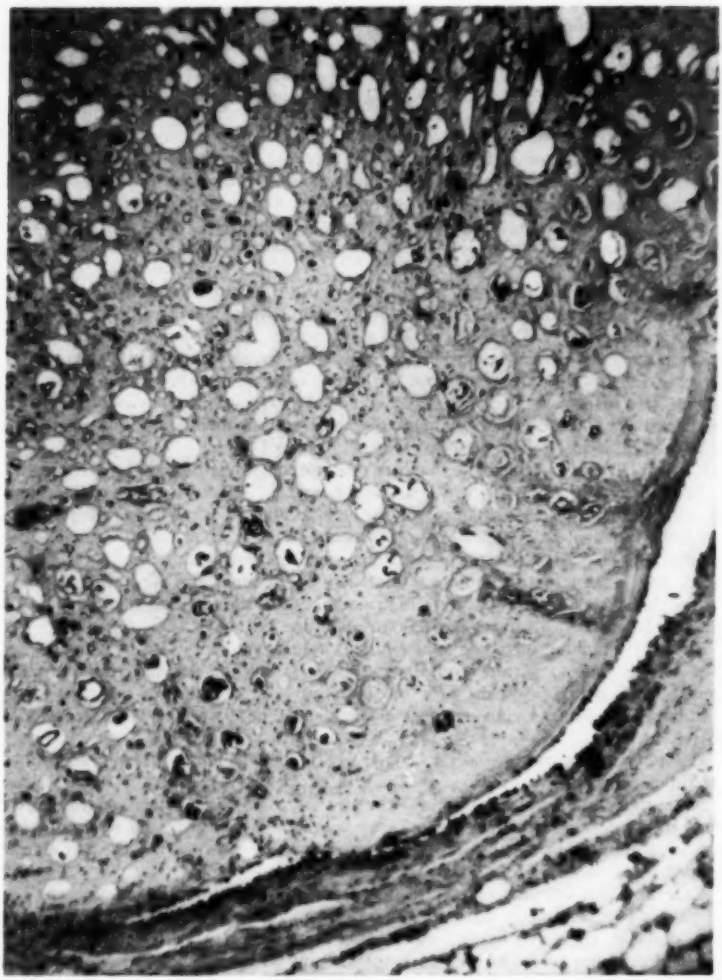

FIG. 3. Tip of pyramid in the stage of healing of papillary necrosis showing epithelization after absorption of necrotic material.

Clinical diagnosis: Hypertensive and arteriosclerotic heart disease III C; diabetes mellitus; anemia.

At autopsy the left kidney was unremarkable except for a 2 cm. cortical adenoma. The right kidney was unremarkable except for the papillae, which were atrophic and fibrotic. The pelvis was not dilated. The ureters were patent. The bladder showed moderate trabeculation, but no evidence of inflammation. Microscopy revealed healed renal papillitis of the right kidney (figure 3).

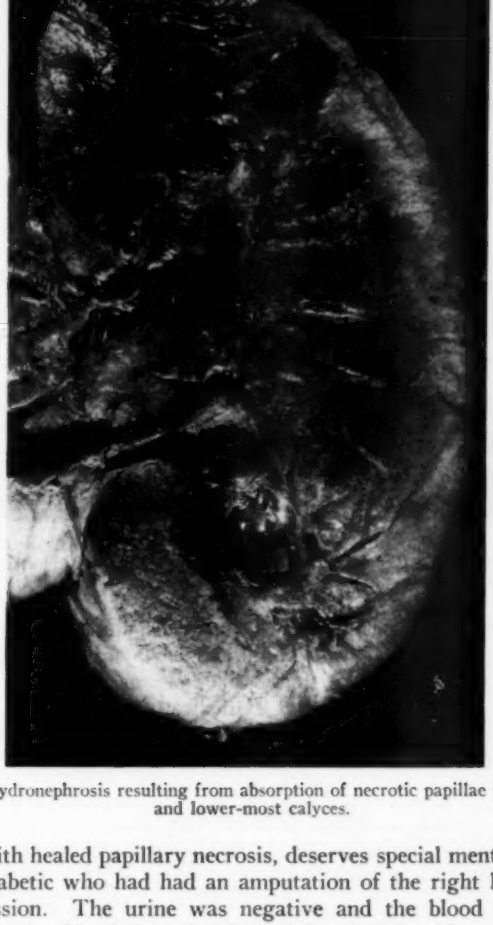

FIG. 4. Note hydronephrosis resulting from absorption of necrotic papillae in the upper-most and lower-most calyces.

Case 8 with healed papillary necrosis, deserves special mention. He was an elderly diabetic who had had an amputation of the right leg one month before admission. The urine was negative and the blood urea nitrogen was not elevated. He died on the eleventh hospital day of a severe broncho-

pneumonia. At autopsy, the right kidney revealed atrophic and fibrotic stumps of papillae. On microscopy the papillae showed a deformed and shortened tip, covered by pelvic epithelium. Many of the collecting tubules near the tip of the papillae were simply empty holes in a hyalin interstitial matrix, but others had an epithelial lining which seemed to be growing downward from the region of the base of the pyramid into the distal collecting tubules.

FIG. 5. Necrotic papillae undergoing resorption. Note the delimited zone of hyperemia at the junction of cortex and medulla suggesting a significant vasomotor component in this pathological process.

It seems evident that such healed absorbed papillae finally give rise to dilatation of the corresponding region of the pelvis of the kidney. Recurrent milder lesions of this type or a single attack of massive necrosis of the inner medulla with final resorption and epithelization offers one demonstrable mechanism for the development of hydronephrosis, particularly obstructive hydronephrosis (figures 4 and 5).

NON-DIABETIC CASES

The five male non-diabetics form a strikingly homogeneous group. They were all over 73 years of age, with an average age of 77. Their illness began a month or more before admission in four cases out of five. The hospital stay was prolonged, ranging from 26 days to 3.5 months, averaging about two months. They all had chronic lower urinary tract obstruction (three

benign hypertrophy and two carcinomas of the prostate). Four of the five had prostatic operations during their hospital stay. All had azotemia. All were moderately anemic, with hemoglobins ranging from 8.5 to 11 grams, and red cell counts from 3 to 4 million. Pyuria was found in four cases, and hematuria in four cases (two gross, two microscopic).

At autopsy all had extensive upper and lower urinary tract inflammatory disease, with cystitis, ureteritis and bilateral pyelonephritis. Only two of the six had advanced necrosis of the papillae—the others revealed limited areas of necrosis within the papillae in areas of acute pyelonephritis.

The lone female had striking bilateral advanced papillary necrosis, but only a moderate urinary tract infection. She had, in addition, a fractured skull, portal cirrhosis and jaundice. The urine was reported sugar free, but a blood sugar was found to be 186 mg. per cent so that this case may well belong to the diabetic group.

Case Reports

Case 1. This 73 year old female fell at home and struck her head. One week later she developed nose bleeds, and jaundice, and was admitted to the hospital. The skin and sclerae were icteric. The liver was palpable one finger's-breadth below the costal margin. Roentgenograms of the skull revealed a fracture in the mastoid region probably extending to the base.

Laboratory data: Urine: albumin 2+, glucose 0, 12 red blood cells per high power field, and 10 white blood cells per high power field. There were no clumps or casts. Hemoglobin 10.5 gm.; red blood cells 3.4 millions; white blood cells 31,100 with 87 per cent polynuclears. Non-protein nitrogen 162 mg. per cent. Blood sugar 186 mg. per cent.

She became comatose, incontinent, and developed projectile vomiting and tarry stools. Her temperature varied from 99° to 101°. She died on the seventh hospital day.

At autopsy the kidneys revealed advanced bilateral papillary necrosis. The microscopic sections demonstrated the classical histology of advanced papillary necrosis (figure 6).

Case 2. This 74 year old white male entered the hospital because of difficulty in urinating during the preceding month. Two weeks before admission he had complete retention and was catheterized on several occasions. On rectal examination, the prostate was enlarged (grade 2), but not hard.

Laboratory data: Urine on admission—albumin 2 plus, glucose 0, microscopically negative. Later specimens were grossly bloody, and contained pus cells. Hemoglobin 8.5 gm., red blood cells 3.1 millions. The blood urea was 15 mg. per cent.

A one stage perineal prostatectomy was performed. Three weeks after operation, necrosis of the anterior rectal wall and the operative site occurred. His condition deteriorated, the blood urea rose to 50 mg. per cent, and he died on the fiftieth hospital day.

Clinical diagnosis: Post-operative perineal prostatectomy with necrosis of anterior rectal wall, sepsis and anemia; arteriosclerotic heart disease.

At autopsy there was a marked bilateral suppurative pyelonephritis, an acute ureteritis, and a hemorrhagic cystitis. On microscopic section the renal papillae showed small circumscribed areas of necrosis of characteristic form.

Case 3. A 78 year old white male entered the hospital with complaints of difficulty in urinating (frequency, nocturia, dysuria) for one month. Rectal examination revealed a fixed, irregular, hard prostate. Temperature 100.2°.

Laboratory data: Urine—albumin 4 plus, glucose 0, acetone 0; microscopic showed red and white blood cells too numerous to count. White blood cells 42,000 with 45 per cent polynuclears. Hemoglobin 62 per cent, red blood cells 3.47 millions. The blood urea was 48 mg. per cent. He ran an irregular fever up to 102.8°. The blood urea rose to 108 mg. per cent. The patient died on the twenty-sixth hospital day.

Clinical diagnosis: Carcinoma of the prostate; uremia.

At autopsy the renal papillae were necrotic. Some were detached and lying free in the pelvis. The pelvis was filled with pus. There was acute necrotizing ureteritis and cystitis. Microscopic sections demonstrated advanced papillary necrosis.

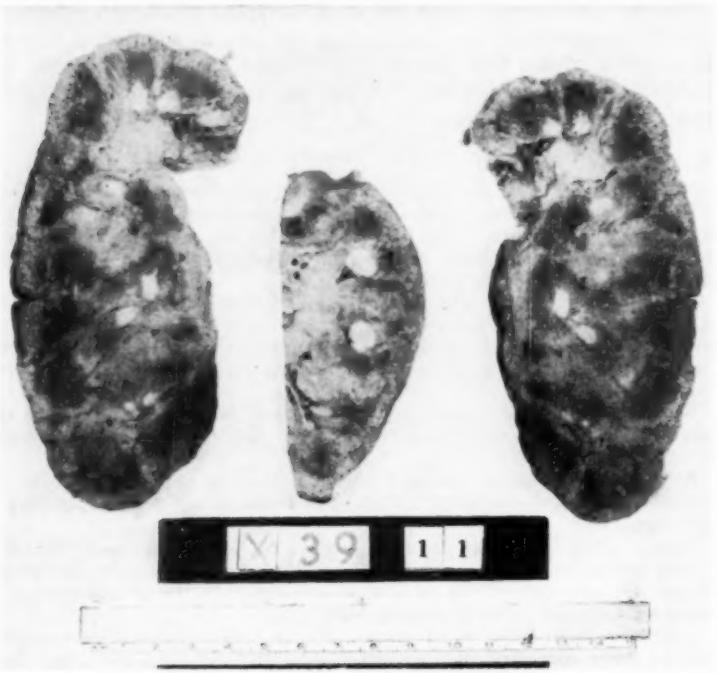

FIG. 6. Section of the kidney of a non-diabetic patient showing gross necrosis of the papillae. Note the sharp limitation of the whitish necrotic zones.

Case 4. This 78 year old white male entered the hospital complaining of inability to void, for the past three days. He had been catheterized once in that interval. There was a three year history of nocturia. Rectal examination revealed 2 plus enlargement of the prostate, which was soft, and not fixed.

Laboratory data: Urine—albumin 4 +, glucose 0 and many red cells with occasional white blood cells. Hemoglobin 7 grams, red blood cells 3.1 million. The white blood cell count rose from 5,000 to 18,000. Blood urea 24 mg. per cent.

A two stage suprapubic prostatectomy was performed, following which he ran a stormy course, with breakdown of the operative wound. He died three and one-half months after admission.

Clinical diagnosis: Benign prostatic hypertrophy; uremia.

At autopsy, bilateral suppurative pyelonephritis, with ureteritis and gangrenous cystitis, was disclosed. Microscopy revealed small areas of non-reactive central necrosis within the papillae.

Case 5. This 77 year old white male entered the hospital with the history of progressive swelling of both legs, which spread to involve the scrotum and abdomen. Dyspnea and orthopnea had been present for the preceding nine months. He had frequency and nocturia. There was no history of diabetes.

Physical examination: Blood pressure 130 mm. Hg systolic and 80 mm. diastolic. The heart was not enlarged, but was fibrillating. Ascites was present. The liver was palpable two fingers below the costal margin. There was 4 plus pitting sacral and leg edema.

Laboratory data: Urine—albumin 0, glucose 0, 40 red blood cells per high power field. Blood urea 29 mg. per cent, blood sugar 125 mg. per cent.

He developed urinary retention which required an indwelling catheter. A spiking fever developed. He was given sulfa drug in small doses. On the nineteenth hospital day sulfa crystalluria with many white blood cells and red blood cells was found. The blood urea rose to 31 mg. per cent. A cystotomy was performed. His condition improved, and he became ambulatory. The blood urea on the thirty-sixth hospital day was 17 mg. per cent. A trans-urethral resection was performed. Following this he developed a shaking chill. Plasma (200 c.c.) was given. The next day he was jaundiced. The blood urea rapidly rose to 65 mg. per cent and then to 124 mg. per cent with 13.6 mg. per cent creatinine. The icteric index was 50. He died on the forty-fifth hospital day.

At autopsy, the kidneys contained multiple abscesses in the cortex. Microscopic sections revealed small areas of necrosis within the papillae, with only marginal reaction.

Case 6. This 81 year old white male was admitted to the hospital because of urinary retention with overflow incontinence. He had had symptoms of prostatism for five years, which had become markedly aggravated within the previous two months (frequency, nocturia, weak stream, etc.).

Physical examination: The bladder was palpated up to the umbilicus. The prostate was 1 plus enlarged, but soft.

Laboratory data: First urine—grossly bloody, albumin 2 plus, glucose 0, blood urea 17 mg. per cent.

A two stage suprapubic prostatectomy was performed. He ran a febrile course. The urine continued to show 2 plus albumin, and white cells. Blood urea rose to 34 mg. per cent. He died on the fifty-second hospital day.

Clinical diagnosis: Benign hypertrophy of prostate; hydronephrosis; pyelonephritis.

Autopsy disclosed multiple cortical abscesses in the kidneys. Papillary necrosis was noted bilaterally. The microscopic sections revealed small areas of necrosis within the pyramids.

Theories of Pathogenesis

A variety of theoretical explanations of the pathogenesis of necrosis of the renal papilla has been advanced.

I. The Rôle of Infection. It is at once apparent that all of the cases occur in association with active pyelonephritis, which is usually suppurative. The toxins of bacteria,[2] the coagulase and necrosin of *Staphylococcus aureus*,[1] and the toxic metabolic products of *B. coli* [18] have all been suggested as factors in the production of the lesion. However, the multiplicity of the bac-

terial flora which is found makes it appear certain that papillary necrosis is unrelated to any specific bacterium.[5] Since no similar necrosis is found in the renal cortex, it is clear that bacterial toxins alone cannot account for the lesion. The bacterial colonies found in the tubules of the necrotic papilla are not simply the result of postmortem proliferation, for Günther [2] found them in surgically removed kidneys as well as in autopsy specimens.

II. The Rôle of Circulation. The blood supply to the pyramid and papilla is poor compared to that of the cortex, being composed of small afferent arterial capillaries and efferent venules lying between the excretory tubules. The infarct-like necrosis which is the chief characteristic of renal papillitis at once suggests vascular occlusion. However, there is no single vessel which could produce such an infarct, and hence the presence of multiple capillary thromboses might be assumed. These are by no means constantly present, or very marked when found; Edmondson et al.[3] noted thrombosis of capillaries in a few kidneys, and extensive thrombophlebitis of the venous system in five kidneys. Davson and Langley [18] found no vascular occlusion. Robbins, S. L., et al.[5] found scattered capillaries containing fibrin thrombi at the base of the pyramid. We have been impressed by the paucity of thrombi in our material. Sheehan [19] suggested the possibility of spasm or acute degeneration of the walls of medullary vessels, such as is seen in cortical necrosis, but the cortical lesion has not been described in cases of papillary necrosis.

The remarkable studies of the renal circulation by Trueta and his colleagues [25] throw new light on many forms of renal disease, and force a reexamination of many old concepts of renal physiology. It is apparent from their work that the kidney has two potential circulations, one through the cortical glomeruli, and one through the juxtamedullary glomeruli and the vasa recta of the medulla. It was found that under certain conditions, blood may pass almost exclusively through one or the other of these renal circuits, thus by-passing the second circuit. The usual circumstance was a by-passing of the cortex via the medullary circuit. In this manner the authors were able to produce bilateral cortical necrosis. The reverse experiment was not performed, but it is of interest to speculate whether, under appropriate conditions, with prolonged medullary ischemia by by-passing of blood into the cortical circuit, it might not be possible to produce the analogue of cortical necrosis, namely necrosis of the renal papillae (figure 5).

It is unlikely, in view of the findings of Trueta's group, that the presence of intracapillary glomerulosclerosis would tend to decrease the blood supply to the renal papilla, as is so commonly supposed, but rather the amount of blood diverted to the medulla may be increased. Further, the degenerative changes in the juxtamedullary glomeruli in elderly persons, culminating in the formation of arteriae rectae verae, all tend to further divert the renal blood flow through the medullary by-pass. Hence, arterial nephrosclerosis may not be considered, theoretically or factually, as a significant factor in compromising the blood supply to the papilla.

III. Mechanical Factors. Robbins, S. L., et al.[5] state that papillary ischemia best explains the occurrence of papillary necrosis. They suggest that the marked inflammatory reaction in the diabetics, and the back pressure of urinary tract obstruction, both operate to further mechanically reduce the anatomically inferior blood supply to the papillae by compression of the

FIG. 7. Micro-photograph showing para-amyloid-like hyalin material in the stroma of the papilla which in this instance bears no direct relationship to necrosis of papillae.

thin wall capillaries. Davson and Langley [18] also discuss the rôle of mechanical pressure, and question why, if pressure on blood vessels were the cause of the necrosis, the lesion is not more often seen in hydronephrosis or nephrolithiasis. Mellgren and Redell [26] consider the deposition of the "para-amyloid" in the interstitial tissue of the renal papillae to play a

mechanical rôle in the production of papillary necrosis, both by pressure and by interference with nutrition of the tubules. We have seen small isolated foci of hyalin material in the papillae of a few of our cases, but have found it more extensively in devitalized papillae of hydronephrotic kidneys, and in sclerotic or senile kidneys than in cases of papillary necrosis (figure 7). The Kimmelstiel-Wilson kidney does not often show papillary necrosis though amyloid-like material is found in increased amounts.

IV. The Rôle of the Diabetic State. The diabetic state in some fashion plays an important rôle in the pathogenesis of this lesion. It is generally considered that diabetics have "less resistance" to infection. The presence of acid bodies in the diabetic urine [18] and the extravasation of acid urine through necrotic tubules [1] have been suggested as possible factors. Harrison and Bailey [6] have demonstrated the frequency of asymptomatic urinary tract infections in diabetics. These authors found, in a series of diabetic patients, that over half had bacilluria, and one-fifth had pyuria; and that bacilluria was six to seven times more frequent, and pyuria five times more frequent in diabetics, than in non-diabetics. It would appear then that this factor of latent infection is more commonly present in the production of papillary necrosis in diabetics than in non-diabetics.

The investigations of Menkin [20, 21] have disclosed certain differences in the inflammatory process in diabetics. The local decrease in pH in inflammation is a lactic acid acidosis produced by increased glycolysis. The increase in local proteolysis in inflammation in diabetes implies increased tissue damage. Gangrene is more common and more severe in diabetics, and papillary necrosis can be thought of as but another example of gangrene in this disease.

V. The Experimental Production of Papillary Necrosis. Attempts to produce papillary necrosis by producing renal infection with urinary tract obstruction have not been successful. Edmondson et al.[1] tied off the ureter in depancreatized rats. The animals developed a pyonephrosis (whereas only hydronephrosis developed in the non-diabetic rat) but papillary necrosis was not found. In their study on experimental pyelonephritis in rabbits, Mallory, Crane, and Edwards [22] do not describe the lesion of papillary necrosis, although Robbins, S. L., Mallory and Kinney refer to its occurrence in such experimental work.

From a study of our material, we conclude that the sequence of events in the appearance of this lesion is an initial rapid, complete infarct-like necrosis of the entire affected region, followed by an inflammatory reaction. This is first seen in varying intensity from minimal to marked, at the junction between the viable and necrotic tissue. There is usually no inflammatory exudate in the area of necrosis but bacterial colonies are commonly found in the lumina of the dead tubules. With disintegration of the necrotic papilla, a diffuse overgrowth of bacteria occurs. We do not believe that papillary necrosis is produced by the coalescence of small abscesses at the base

of the pyramid with distal ischemic infarction, as described by Robbins, S. L., Mallory and Kinney.

Comparison with necrosis of the papillae produced by chemical poisons [23, 24] confirms the above interpretation, that the lesion is produced by death of tissue en masse, followed by a variable amount of reactive inflammation and bacterial proliferation. Certain specific chemical poisons have successfully produced papillary necrosis in the experimental animal. Levaditi [23] produced the lesion in rabbits, guinea pigs and mice by subacute poisoning with vinylamin. Rehns [24] produced the lesion in rabbits and guinea pigs, but not mice or rats, by administration of tetrahydroquinoline and its methyl esters. The mode of action of these chemicals, and their relation, if any, to fat metabolism, are unknown to us.

The experimental production of papillary necrosis in rats by a fat-free diet has been detailed earlier in this report. It was shown by Burr and co-workers that the deficiency is chiefly one of unsaturated long chain fatty acids; that a very small amount of these may restore normal fat metabolism; and that although the fat-deficient animals synthesize fat, they cannot synthesize the necessary long chain unsaturated fatty acids. It may be very significant that in diabetics there exists a profound disturbance in fat metabolism, with uncontrolled overproduction of fatty acids. The non-diabetics we have studied were all elderly men with chronic urinary tract obstruction and infection, with anemia and azotemia, all of which were additive in producing debility and malnutrition, with its accompanying disturbance of fat metabolism (e.g., "starvation acidosis"). E. M. Boyd [27] found that during fever neutral fat increases 50 per cent, but total and free cholesterol and phospholipids fall, after an initial rise. He noted that the iodine number of plasma fatty acids fell markedly after an initial rise.

It may be said, then, that disturbed fat metabolism is a common factor in diabetes; in non-diabetics with debility, malnutrition, and sepsis; and in the experimental animal on fat-free diet. It is not possible to say at this time whether a deficiency in unsaturated fatty acids plays a direct rôle in the pathogenesis of papillary necrosis, or whether it plays an indirect rôle by inducing alterations in renal hemodynamics, or in the responses to infection.

Although azotemia is commonly found in patients with this lesion, it cannot be the primary mechanism, for papillary necrosis is not commonly found in diseases that produce uremia most commonly, i.e., arteriolar nephrosclerosis, chronic glomerulonephritis, and chronic progressive pyelonephritis. Uremia and azotemia undoubtedly do play a significant part in the debility and malnutrition of these cases. Further, in diabetics, the illness may be fatal within a far shorter time than is found in uremia. It would seem that azotemia and uremia contribute to the lesion but are not its causes, and rather may be caused by it.

Papillary necrosis is not invariably fatal, for healing does occur, as is demonstrated in our case 8; in a case reported by Edmondson et al.[1]; and in

a case described by Günther [2] the course of which was followed by means of retrograde pyelograms over a period of six months.

Nephrectomy has been performed in several instances of this disease. In two operated diabetics reported by Robbins, S. L., et al.,[5] the patients were alive and apparently free of renal disease one year later. In three surgically treated diabetic cases reported by Günther,[2] one died eight weeks later, but the other two survived. Mellgren and Redell [20] describe a case in which the surgically removed kidney showed extensive papillary necrosis. The remaining kidney, at autopsy some time later, revealed much less extensive necrosis of the papillae.

It is unlikely that all of the nephrectomized diabetic patients who survived had only unilateral lesions. It is far more probable that some had bilateral lesions which went on to healing in the remaining kidney. We have seen several cases at autopsy which suggested a preëxisting necrotic papillitis in the form of reticulated or spongy fibrous remnants. The several cases of this group presenting very suggestive transition features are not included in this study of the fully developed acute lesion.

Summary

1. Necrosis of the renal papillae is a striking pathological lesion which is found in association with acute pyelonephritis in diabetics, and in non-diabetics with urinary tract obstruction.

2. The clinico-pathological findings in 13 acute and one healing case are reviewed.

3. The diabetic patients as a group are younger, have a shorter clinical course, and may present themselves in coma. This may have the appearance of diabetic coma, but acetonuria may be absent. The sex incidence of two females to one male is apparently not explained by higher incidence of diabetes in the female.

4. The non-diabetic patients are older, have a more prolonged clinical course and are usually males with prostatism and urinary tract infection.

5. Experimentally, this lesion has been produced by specific chemical poisons, and by fat-free diets whose essential defect appears to be the absence of certain long chain unsaturated fatty acids.

6. A parallelism is suggested between the disturbed fat metabolism in diabetics, in non-diabetics with urinary tract obstruction and sepsis, and in experimental fatty acid deficiency.

7. It is suggested that papillary necrosis may well be the homologue of cortical necrosis of the kidney on the basis of altered hemodynamics, as indicated by the work of Trueta, with spasm of the medullary vessels rather than the cortical vasculature as the significant factor in the mechanism.

8. Necrosis of the pyramids can go on to complete healing. A single or multiple recurrent attacks of such papillary necrosis, with subsequent healing and epithelization, may represent one mechanism of hydronephrosis.

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THE SURGICAL TREATMENT OF BLEEDING ESOPHAGEAL VARICES BY PORTAL SYSTEMIC VENOUS SHUNTS WITH A REPORT OF 34 CASES *

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ESOPHAGEAL varices develop spontaneously because of obstruction to the return of the portal blood to the systemic venous system. The site of the portal bed block may be either in the liver, the intrahepatic type secondary to portal cirrhosis, or in the portal vein itself, the extrahepatic type, as seen in the so-called Banti's syndrome (table 1). The block in the former develops as a result of scarring in the liver parenchyma. It occurs most frequently in cases of alcoholic and other forms of toxic cirrhosis and is the more common type. Thrombosis of the hepatic vein is another cause of the intrahepatic type of block. It is relatively rare, however. The portal bed block in the extrahepatic type may result from a congenital obliteration of the portal vein

TABLE I

Types and Etiology of Portal Bed Block
(Massachusetts General Hospital)

I. Intrahepatic
  A. Portal cirrhosis (Laennec type)
    1. With cavernomatous transformation of portal vein
    2. Without cavernomatous transformation of portal vein
  B. Thrombosis of hepatic veins
II. Extrahepatic (Banti's syndrome)
  A. Congenital—oblit. of portal v. with cavernomatous transformation
  B. Acquired—thrombosis of the portal vein or its tributaries
  1. Infectious 2. Traumatic 3. Spontaneous
III. Combined type
  Portal cirrhosis with portal vein thrombosis

or arise secondary to thrombophlebitis of the portal venous system, the etiology of which may be traumatic, infectious or idiopathic. A combined form of the intrahepatic and extrahepatic types has been found in a certain number of cases. In this group of patients a thrombophlebitis of the portal venous system has apparently developed secondary to the intrahepatic block due to cirrhosis of the liver. Whipple [1] describes another form of extrahepatic block, the so-called cavernomatous transformation of the portal vein, which is thought by some authorities to represent a vascular neoplastic lesion, an angioma in the hepatoduodenal ligament. It seems more likely, however, that the innumerable small blood vessels encountered in this region probably represent collateral channels that have developed as a result of the block in

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the portal venous system, since this type of vascular pathology has been found both in the intra- and extrahepatic groups.

The normal venous pressure in the portal system is higher than in the systemic veins because the portal blood after passing through the capillaries of the gastrointestinal tract, spleen and pancreas must traverse another capillary bed, the liver sinusoids, before it enters the inferior vena cava. The normal portal venous pressure has been found to be 10 to 15 cm. of saline. In the presence of portal bed block, either intra- or extrahepatic, the state of so-called portal hypertension develops with pressures varying from 25 to 50 cm. of saline. One of the collateral channels whereby the portal blood returns to the systemic venous system in these conditions is the esophageal veins. These vessels do not anastomose freely with the systemic system so that they frequently become greatly enlarged and varicosed. Hemorrhage from them is a common complication of portal hypertension and carries with it a very high mortality rate. The cause of rupture of these blood vessels has not been satisfactorily explained, but in part it is believed due to the relatively high venous pressure within them. Wangensteen [2] has suggested that it may be due to peptic ulceration of the esophageal mucosa over them, because of the reflux of acid gastric contents into the esophagus.

Diagnosis

The diagnosis of bleeding esophageal varices should be considered along with the other causes of esophageal-gastrointestinal bleeding in any patient who gives a history of hematemesis or melena. A sudden massive hematemesis is frequently the first sign that a patient has a portal bed block, especially of the extrahepatic type, since there are few premonitory symptoms of the disease. The diagnosis of a portal bed block with esophageal varices is suggested by such a history, especially if an enlarged spleen is found on physical examination. The blood, as a rule, shows a secondary anemia, a leukopenia and a thrombocytopenia. If the block is intrahepatic the liver may be shrunken, normal or enlarged and in the extrahepatic it is usually normal in size. The two types may be further differentiated by liver function tests. When the block is intrahepatic, there is usually a high retention of bromsulfalein, a reversal of the albumin-globulin ratio with a low level of serum albumin, a positive cephalin flocculation test and an elevated prothrombin time. If the block is extrahepatic all these liver function tests are usually normal. The most important diagnostic procedure, however, in patients suspected of having bleeding esophageal varices is a roentgenologic examination of the esophagus with a thick suspension of barium, as first described by Wolf [3] and later Schatzki [4] (figure 1). The visualization of the blood vessels by this technic depends to a great extent on the skill of the roentgenologist. Direct visualization of the lower end of the esophagus by esophagoscopy is another aid in diagnosis. The demonstration of esophageal

varices by either of these methods indicates the presence of portal hypertension secondary to either an intra- or an extrahepatic portal bed block.

The frequency with which bleeding occurs from esophageal varices has been variously reported. Preble [5] in 1900 in reviewing 60 cases of fatal gastrointestinal bleeding found that 80 per cent had esophageal varices. Macroscopic evidence of rupture of these vessels was demonstrated in 50 per cent. Rivers and Wilbur [6] in 1932 reported that in a group of 668 patients with a history of hematemesis the bleeding was secondary to cirrhosis of the

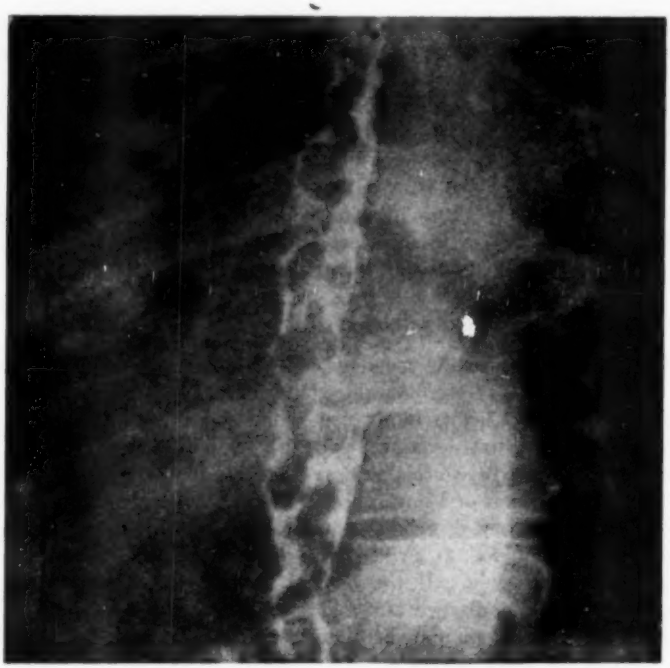

FIG. 1. A reproduction of a roentgenogram of the esophagus demonstrating the esophageal varices in a patient with portal hypertension due to so-called Banti's syndrome. This diagnostic procedure affords the most positive diagnosis of portal hypertension.

liver, or splenic anemia (Banti's syndrome), in 33, or 5 per cent. A recent analysis by Costello [7] in 1949 of 300 consecutive cases of massive hematemesis reveals that 24, or 8 per cent of the series, had ruptured esophageal varices as the cause. It is extremely significant and pertinent to this discussion that 19 died from hemorrhage, a mortality rate of 71 per cent, in this group.

Shull [8] in 1947 studied 108 patients with cirrhosis of the liver and 20 patients with Banti's syndrome that were admitted to the Massachusetts

General Hospital over a 12 year period from 1934 to 1945. He found that in the cirrhotic group only 40, or 37 per cent, were alive one year after the diagnosis of esophageal varices was made. In the Banti's syndrome group 18, or 90 per cent, were alive. This higher mortality rate in the patients with cirrhosis is due undoubtedly to the fact that the patients are in an older age group. In addition and of extreme importance is the fact that they for the most part have severely damaged livers, whereas the Banti's group are relatively young and have essentially normal livers. Shull [8] in these same patients found that in the cirrhotic group 90, or 83 per cent, died from all causes. Of extreme significance, however, he found that 41, or 45 per cent, of those that died succumbed to massive esophago-gastrointestinal hemorrhage. In the Banti's group, seven, or 35 per cent, died from all causes and of these five, or 71 per cent of the deaths were due to hemorrhage. The mortality rates from hemorrhage alone in all the patients of the two groups were 38 per cent for the cirrhotics and 25 per cent for the Banti's syndrome group. In addition it is believed that hemorrhage was an important contributing factor in the death of many of the other patients who died from liver failure and other causes. This is especially apt to be true in a group with intrahepatic block, because in many of these patients the serum albumin level is already low due to the liver disease, and as a result of the severe hemorrhage a further rapid reduction takes place. Moreover in the presence of a diseased liver restoration of the serum albumin to a normal level seldom occurs.

The analysis of these cases is of great significance, since it demonstrates the grave prognosis once esophageal varices are diagnosed and the high mortality rate due to hemorrhage from them. At best bleeding esophageal varices cause prolonged disability, since patients after severe hemorrhage frequently require many weeks to months of hospitalization with expensive therapeutic measures. Numerous blood transfusions are essential in many cases to prevent death from shock, and in some cases the blood escapes almost as fast or faster than it can be administered. Under such conditions the bleeding may only be stopped by the placing of a balloon in the stomach which, after inflation, is drawn up against the cardia by means of traction on the rubber tube to which the balloon is attached, as reported by Rowntree et al.[9]

The realization of this high morbidity and mortality due to the bleeding from esophageal varices has spurred us on in an attempt to lower the portal hypertension and reduce the amount of blood in the esophageal varices by formation of various types of portal systemic venous shunts. The treatment of bleeding esophageal varices by various surgical procedures has been attempted for many years. The demonstration by Eck [10] in 1877 that the portal venous blood could be shunted directly into the systemic venous system by anastomosing the portal vein directly to the inferior vena cava in experimental animals, thereby by-passing the liver, stimulated surgeons in the latter part of the 19th century and the early part of the 20th century to perform

a similar type of shunt in human patients. Few were successful, presumably because of the high mortality rate from the operative procedure, so that this method of treatment was abandoned for several decades. It was not until the recent work of Whipple [1] and Blakemore and Lord [11] in 1945, who reported the successful construction of portacaval shunts, that surgeons became interested again in this relatively unexplored field in vascular surgery. These authors first described an end-to-end splenorenal type of shunt, utilizing the nonsuture type of blood vessel anastomosis with the vitallium tube method of Blakemore and Lord.[11] In addition to performing a splenectomy at the same time, it was also necessary to sacrifice the left kidney in order to perform this type of a shunt.

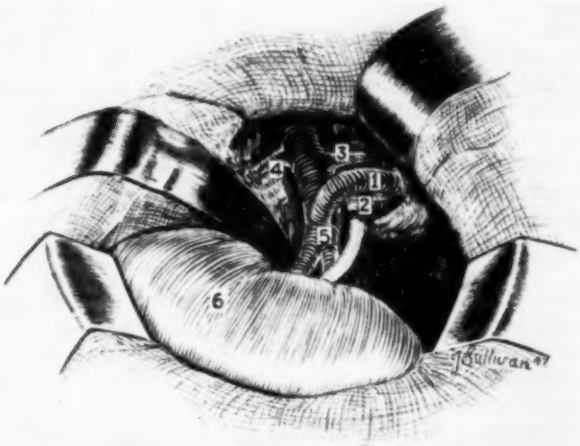

FIG. 2. An artist's drawing showing the completed end-to-side suture type of splenorenal anastomosis with preservation of the left kidney. 1. splenic vein; 2. renal artery; 3. suprarenal vein; 4. spermatic vein; 5. renal vein; 6. left kidney. (Courtesy Surg. Clin. N. Am., W. B. Saunders Co., 1947, xxvii, 1162.)

The above procedure has been modified by the construction of an end-to-side splenorenal anastomosis with preservation of the kidney, as previously reported [12, 13] (figure 2). This operation is preferred, first because it produces a partial shunt of the portal blood flow, so that the liver is not completely by-passed. Second, because our observations indicate that this type of shunt appears to lower satisfactorily the portal hypertension. Third, the splenectomy reduces the arterial inflow to the portal area by approximately 20 to 40 per cent and thereby aids in the reduction of the portal hypertension. Fourth, the end-to-side type of anastomosis in addition to preserving the kidney has the advantage that it is less apt to become thrombosed. Fifth, it can be constructed by the suture technic instead of the nonsuture vitallium

tube method, thereby reducing the incidence of thrombosis at the site of the anastomosis. Sixth, there are no vital structures in the left upper quadrant of the abdomen, the region through which the surgical approach is made for this type of shunt, similar to the common bile duct or the hepatic artery which lie in such close proximity to the region where it is necessary to dissect out the portal vein and the inferior vena cava to perform a direct portacaval anastomosis. This last is a point of great practical importance since in either type of shunt operation structures are obscured frequently by bleeding from innumerable small collateral venous channels. An error of a few millimeters in the region of the gastrohepatic ligament in searching for the portal vein may irreparably damage the common bile duct or the hepatic artery with serious consequences, whereas in the splenic area such catastrophes are not as likely to occur since the margin of safety in this region can be measured in centimeters rather than millimeters.

During the past four years at the Massachusetts General Hospital from 1945 to 1948 inclusive, 34 patients with portal hypertension have had various types of portal systemic venous shunts constructed by the suture technic for bleeding esophageal varices. These operative procedures have not been performed on patients unless there was a history of esophago-gastrointestinal bleeding, nor have they been done for the relief of ascites alone. It has been considered advisable in developing this new type of surgery to subject only those patients in whom severe or repeated hemorrhages have taken place in an attempt to see whether future bleedings could be prevented. In this group of patients there were 20 with the intrahepatic type of portal bed block due to cirrhosis of the liver and 14 patients with Banti's syndrome, or congestive splenomegaly, the extrahepatic type of portal bed block. The youngest patient in the group was six years of age and the oldest 65 years. Both had the extrahepatic type of portal bed block, the former presumably of congenital origin due to obliteration of the portal vein and the latter due to thrombosis of the portal venous system of idiopathic origin. The mean age in this group was 36 years. The ages of the intrahepatic group due to cirrhosis of the liver ranged from 27 years to 60 years with a mean age of 44 years. Seven patients in the latter group died as a result of the operative procedure, a mortality rate of 35 per cent. There were no deaths in the Banti's syndrome group, making an operative mortality rate of 21 per cent for the entire group. It is of interest that the operative mortality rate has dropped with the increased experience gained in this type of surgery and the better selection of patients for the procedure, since 20 patients were operated upon in the year 1948 with two deaths, an operative mortality rate of only 10 per cent. Both of them occurred in the cirrhotic group. These statistics indicate, as might be expected, that the risk of this type of surgery which frequently requires four to six hours of anesthesia is greater in those patients with cirrhosis because of the underlying liver disease.

An analysis of the causes of death in these seven patients reveals that four of them died within a few hours of uncontrollable hemorrhage from the

site of operation due to a state of incoagulability of the blood. The preoperative prothrombin times were normal in all these patients and for the first two hours of the operation in each case there was no evidence of the failure of the patient's blood to clot. However, after varying periods from two to three hours after the operation was commenced it was noted that blood began to ooze from all the cut surfaces of the operative site. Samples of blood collected in test tubes failed to clot for many hours and when these were recalcified there was still no evidence of clotting, indicating that it was not caused by the sodium citrate in the blood transfusions. Further studies are in progress at the present time in an effort to determine the cause of this phenomenon which ended so disastrously in these four patients. All of them had severely damaged livers from cirrhosis. Because of this a more careful selection of patients is now made, especially in reference to the condition of the liver, in an effort to prevent similar tragedies, as Blakemore [14] has also stressed. The other three patients died from various causes: one from massive esophageal bleeding five days following an anastomosis of the superior mesenteric vein to the inferior vena cava. (At operation in this case the superior mesenteric vein was obviously not of sufficient caliber to lower satisfactorily the portal hypertension.) Another case died 48 hours postoperatively from liver failure; the third one in 48 hours, secondary to thrombosis of the hepatic artery. This group of seven deaths is extremely regrettable but when it is realized that most of these patients were extremely ill and were operated on as a last resort in an attempt to save their lives, it is not too surprising that some of them did not survive a surgical operation of the magnitude of these shunt procedures.

A splenectomy with an end-to-side suture type of splenorenal anastomosis has been the most common type of shunt performed in our clinic. It was performed in 26, or 74 per cent, of the patients. There were four postoperative deaths, an operative mortality of 15 per cent. Twenty-two patients, or 85 per cent, survived the operation. One patient, a man aged 60, with cirrhosis of the liver, succumbed to liver failure secondary to alcoholism eight months following the formation of the splenorenal shunt. He had not bled since it was performed and postmortem examination revealed a satisfactory patent venous anastomosis without evidence of old or recent thrombosis. Esophago-gastrointestinal bleeding has occurred in one of the 21 surviving patients, an incidence of postshunt bleeding of approximately 5 per cent. This patient is one of the Banti's syndrome group and was the first one on whom the splenorenal type of shunt was performed. The bleeding followed an overindulgence in food and alcoholic beverages. Another factor in this patient which might explain the postoperative bleeding was that the end-to-side splenorenal anastomosis was of inferior construction as it was the first one performed. Moreover great technical difficulties were encountered at the operation, due to the fact that there had been three previous operative procedures, including first: a ligation of the splenic artery and an omento-

pexy; second, ligation of the coronary vein of the stomach and a second omentopexy; and third, a transthoracic ligation of the peri-esophageal veins.

A direct portacaval shunt, the Eck type of fistula, anastomosing the portal vein to the inferior vena cava was attempted in eight patients. It was possible to perform it in only three of them because in the other five the extreme vascularity in the region of the gastrohepatic ligament prevented exposure of the portal vein. In one patient the common bile duct and gall bladder were injured, necessitating a choledochojejunostomy to reëstablish the flow of bile into the intestinal tract and also a cholecystectomy. This patient at a later operation had a splenectomy and a satisfactory end-to-side splenorenal shunt performed. The direct portacaval type of anastomosis was chosen in these eight patients for various reasons. Splenectomy had been previously performed in five of them, which has been found to preclude the construction of a splenorenal shunt at a later date because of thrombosis and secondary fibrosis of the splenic vein. For this reason it was necessary to attempt some other form of shunt in these patients and the direct portal vein to inferior vena cava type of anastomosis was chosen. In two other patients this procedure was selected because the spleen in both was only slightly enlarged, indicating that the splenic vein would not be large enough with which to create a shunt of sufficient size to reduce the portal hypertension. In the remaining patient it was chosen because three other surgeons who had operated upon him had considered a splenectomy to be too formidable a procedure to perform, so that a direct portacaval shunt was attempted almost of necessity. It is of interest that the portal bed block was intrahepatic in three of the patients and extrahepatic in the other five. Two of the patients died; one in whom the shunt was constructed succumbed because of thrombosis of the hepatic artery, the result of operative trauma. In the other one the operation had to be discontinued even before the portal vein was exposed because of uncontrollable bleeding in the operative field and despite numerous transfusions the patient died from postoperative hemorrhage. Both of these patients had the intrahepatic type of portal bed block with severe impairment of liver function from portal cirrhosis, which undoubtedly played some rôle in their deaths.

A successful portacaval anastomosis with survival was performed in only two of the patients, one with intrahepatic block and the other of the extrahepatic type. Both of these patients had had previous splenectomies without relief from massive bleeding. It is at least encouraging that they are alive and have had no further esophago-gastrointestinal hemorrhages for periods of six months in one case and 12 months in the other. The difficulty encountered in attempting to perform a portal vein to inferior vena cava shunt in patients with the so-called Banti's syndrome, the extrahepatic type of portal bed block, who have had previous splenectomies cannot be over-emphasized, as has already been reported,[15] since in four of these previously splenectomized patients it was possible only in one to create a satisfactory shunt.

In view of these facts and also the good results obtained to date with splenorenal shunts, it should be stressed that a surgeon, who does a splenectomy for portal hypertension, especially for patients with Banti's syndrome, should perform a splenorenal anastomosis at the same operation, since this may be the only opportunity for the construction of a satisfactory shunt.

It is of interest also that in three patients, previously splenectomized, in whom a direct portacaval anastomosis was impossible, other types of shunts have been performed (figure 3). An anastomosis between the proximal end

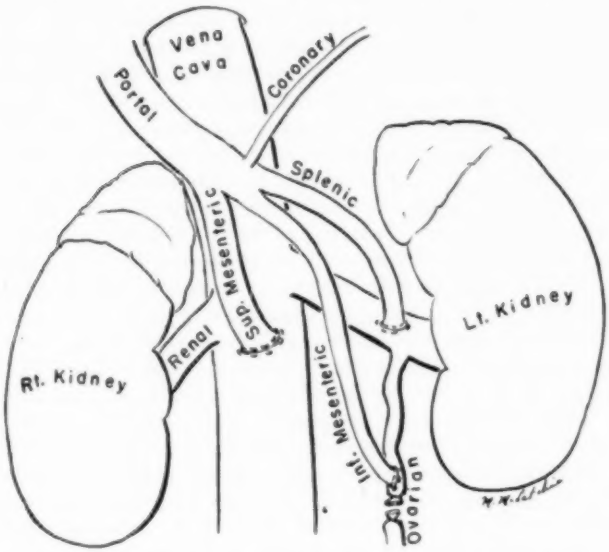

FIG. 3. An artist's schematic drawing showing various types of portal systemic venous shunts. The end-to-side splenorenal anastomosis is preferred, but in two patients who had had previous splenectomies a superior mesenteric to inferior vena cava anastomosis was performed in one and in the other an inferior mesenteric to left ovarian vein anastomosis was used because it was not possible to isolate the portal vein in either due to the extreme degree of vascularity in the gastrohepatic ligament. (Courtesy Surg., Gynec. and Obst., 1948, lxxxvii, 129.)

of the superior mesenteric vein at the base of the mesentery and the inferior vena cava was performed in one of these patients. In another the inferior mesenteric vein was anastomosed to the left adrenal vein and in a third this vessel was anastomosed to the left ovarian vein. These types of shunts are considered to be makeshift ones at best, since these tributaries of the portal vein are too small to produce an anastomosis of sufficient size to reduce the portal hypertension satisfactorily. Nevertheless, although all three patients have had further esophago-gastrointestinal bleeding episodes, they have been

improved since the postshunt episodes of hemorrhage have not been as severe as the prior ones.

In summary, it can be stated that the construction of various types of portal systemic venous shunts represents a new chapter in the treatment of bleeding esophageal varices, a condition which heretofore has failed to respond to other forms of treatment. In the four year period from 1945 to 1948 inclusive, 34 patients at the Massachusetts General Hospital have been subjected to this type of surgery because of the chief complaint of massive esophago-gastrointestinal hemorrhages. The chief benefit from this type of procedure, that has been observed to date, has been the cessation of bleeding in a majority of patients that have had a satisfactory shunt performed, either a direct portacaval or a splenorenal type. There are 24 patients in this group that can be classified in this category and only one of them has bled since the operation was performed, an incidence of only 4 per cent of bleeding.

The postoperative follow-up studies in reference to liver function at present are incomplete. The bromsulfalein retention test and the serum albumin level in the cirrhotic group of patients reveals little if any improvement in these functions of the liver. In the Banti's syndrome group, they reveal little if any impairment following the construction of the shunt. The cephalin flocculation test in the majority of the cirrhotic patients shows slight improvement from 4 +–3 + to 3 +–2 +. The most striking improvement has been in the level of the hemoglobin, as would be expected, since esophago-gastrointestinal bleeding has ceased in the majority of patients. The preoperative levels varied from 7.4 to 12.4 grams of hemoglobin per 100 cubic centimeters of blood and the postoperative levels have been maintained at from 11 to 17.5 grams of hemoglobin. The period of postoperative follow-up is of necessity short, but it ranges from four to 34 months. A true evaluation of the procedure necessarily must await a greater lapse of time, but at the present writing the results are definitely encouraging.

Conclusions

1. The establishment of portal systemic venous shunts represents a new and encouraging chapter in the treatment of bleeding esophageal varices secondary to portal hypertension.

2. Splenectomy and the suture type of end-to-side splenorenal anastomosis with preservation of the kidney is recommended as the most satisfactory operative procedure.

3. It is believed that a surgeon should not do a splenectomy in a case of portal hypertension unless he is prepared to do a splenorenal anastomosis at the same operation, since this may be the only opportunity to construct a satisfactory portal systemic venous shunt.

4. The postoperative studies over periods of 4 to 34 months in patients in whom satisfactory portal systemic venous shunts have been performed

reveal an encouraging cessation in bleeding from the esophago-gastrointestinal tract and the maintenance of normal hemoglobin levels in the blood.

5. A true evaluation of this method of treatment for bleeding esophageal varices, secondary to portal hypertension, must await a longer period of observation of the patients that have been treated by this method.

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PHARMACODYNAMICS OF PULMONARY ABSORPTION IN MAN. II. THE INFLUENCE OF VARIOUS DILUENTS ON AEROSOL AND INTRATRACHEAL PENICILLIN *

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THE pharmacodynamics of pulmonary absorption has not been generally considered in the clinical reports on the success of aerosol and intratracheal therapy. There is equally meager information regarding the action of various pharmacologically active diluents in promoting or retarding absorption of penicillin from the pulmonary epithelium.

In a recent study [1] we described various factors influencing absorption from the normal human lung. Crystalline penicillin G potassium (100,000 units) in physiologic saline was administered intramuscularly, intratracheally and by oxygen-aerosolization. The blood levels and urinary excretion, following intratracheal injection, were lower but more sustained than those following intramuscular administration. Rapid absorption would normally be expected from such a large and vascular area as the alveolar bed. The lung was thus demonstrated as a reservoir capable of considerably retarding the expected rate of absorption. By comparing the total urinary excretion of the intratracheal with aerosol method of administration, the amount of penicillin actually reaching the lung by the latter route was calculated to be about 35 per cent. Easily determinable wastage, occurring during aerosolization, accounted for some of the loss.

Although physiologic saline has been most generally used as the diluent or vehicle for penicillin aerosolization, other diluents, which are active substances themselves, have been suggested. Inhalation of 0.5 to 1 per cent adrenalin has been notably effective in relieving bronchospasm in the asthmatic,[2, 3] neosynephrin is a potent bronchovasoconstrictor which shrinks mucous membranes rapidly. Combination of either or both of these two solutions with penicillin was a natural development when the need arose for such medication in addition to penicillin itself. While such vehicles have been used with penicillin, others suggest themselves as effective diluents because of their inherent pharmacological activity. The search for diluents which might either enhance or supplement the action of penicillin or act independently to advantage has attracted relatively few investigators.

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Methods

The study was done with the help of normal male volunteers. A standard dose of 100,000 units of crystalline penicillin G potassium was used. Two routes of administration were investigated: intratracheal and inhalational. The technic of administration by each of these routes was the same as previously described.[1] For aerosol administration penicillin was dissolved in 1 c.c. of the diluent. After complete aerosolization, another 0.5 c.c. of the diluent or saline was added to salvage any penicillin clinging to the wall of the nebulizer. We chose this technic, rather than multiple rinsings, to more closely simulate clinical conditions. The Vaponefrin nebulizer was used throughout with an oxygen flow of 5 liters per minute. For intratracheal injection, the penicillin was dissolved in 10 c.c. of the diluent. Diluents with sympathomimetic action were given in lower concentrations by this route than by the aerosol one. Following inhalation, serum was assayed for penicillin activity at the end of one-half, one and two hours; urine specimens, at one, two and 24 hours. Following intratracheal administration, bloods were taken at one-half, one and every hour thereafter for six hours and urine specimens were collected at one, two, four, six and 24 hours.

Using the hemolytic streptococcus No. 98, the serial dilution method of Rammelkamp [4] was employed. The smallest amount of penicillin detectable by this method is 0.02 unit per c.c. of serum. The limits of its accuracy are similar to other methods of biological assay involving serial dilution; each level indicates about one-half as much activity as a positive reaction occurring in the next higher tube. The values are obtained by serial half dilution dividing the number of units per c.c. of standard (20 by 2), i.e. 10, 5, 2.5, 1.25, 0.625, 0.312, 0.156, 0.078, 0.039, 0.019. For purposes of simplicity, we employ values numerically expressed as 0.63, 0.32, 0.16, 0.08, 0.04, etc. A level of 0.04 (0.039) unit of penicillin per c.c. of serum, by this method, inhibits most gram-positive pathogenic organisms.[5]

A total of 837 specimens were assayed—468 sera and 369 urines. The following diluents were studied: saline, neosynephrin, epinephrine, tri-ethylene glycol, chlorophyll, Pantopaque and human serum. These are divided into two main groups: (1) those whose predominant action is on the musculature and vascular bed of the lung, thereby secondarily affecting penicillin absorption, and (2) those which influence absorption by direct chemical or mechanical action. Any one substance may easily influence absorption by a combination of these mechanisms. Each solution is classified, however, according to its presumed predominant effect. Even though the pulmonary vessels are considered to be less responsive to vascular agents than other vessels,[6] substances such as neosynephrin and epinephrine may still be expected to exert some influence on the absorptive mechanism. The other substances studied, as far as is known, do not exert any marked effect on the mucous membranes. Thus, any change in the rate of absorption or excre-

tion occurring with their use must be attributed to a local chemical or mechanical action.

Results

For an analysis of data in terms of therapeutic effectiveness, the bactericidal activity in vitro must be correlated *with* clinical or in vivo results. The average minimal effective level at which most gram-positive pathogens are killed faster than they multiply, or the concentrations at which these organisms fail to grow in culture, is 0.04 (0.039) unit of penicillin per c.c. of serum. For purposes of analysis, therefore, we elected to call this the "minimum therapeutic level." This, and higher levels, we have called "positive"; levels less than 0.04 unit per c.c. of serum we have called "negative."

Following aerosolization of penicillin in each diluent, serum levels were evaluated according to the above criteria. The overall effectiveness of a diluent was judged by the following determinations. First, by the number of sera at or exceeding 0.04 unit per c.c. throughout the entire two hours;

Chart I

Diluent	Physiologic Saline	Neosynephrin (1%)	Epinephrine (1%)	Triethylene Glycol (100%)	Chlorophyll (100%)	Pantopaque (100%)
No. of sera tested	36	35	33	33	27	26
Total percentage of positive sera*	69	66	33	18	44	11
Percentage of sera still positive at the end of two hours	25	45	9	9	0	11
Percentage of sera exceeding minimum therapeutic level	39	29	9	9	22	0

* 0.04 unit or more.

this is expressed as the *total percentage of positive sera* for each vehicle. Second, by the ability of any particular diluent to affect absorption so that blood levels are positive for a longer period of time; this is reflected in the *percentage of sera still positive at the end of two hours.* Third, by the *percentage of sera whose penicillin activity exceeds the minimum therapeutic level* (i.e. more than 0.04 unit per c.c. of serum). Determination of the latter is important since the "minimum therapeutic level" is insufficient for complete bactericidal activity against many strains of susceptible organisms. Diluents which will so affect absorption that levels in a higher range result, must, therefore, be considered particularly effective. A summary of each aerosolized diluent analyzed according to these criteria is given in chart 1.

Neosynephrin is a potent bronchovasoconstrictor with poor bronchodilator properties; epinephrine has less vasoconstrictor properties but is a

CHART II

Tabulation of Blood Levels and Urinary Excretion Following the Inhalation of 100,000 Units of Crystalline Penicillin Potassium (C.S.C.) in Various Diluents in Normal Males

Hours After Dose	Penicillin, units per c.c. serum				Number of Sera Tested	Per Cent Positive Sera*	Urinary Excretion (Averages)
	<0.04	0.04	0.08	0.16			
Physiologic Saline							
½	1	4	5	2	12	92%	
1	1	5	6		12	92%	3,053
2	9	2	1		12	25%	922
24							574
Total	11	11	12	2	36	69%	4,549
Neosynephrin 1%							
½	2	4	5	1	12	83%	
1	4	4	4		12	66%	2,807
2	6	5			11	45%	1,526
24							195
Total	12	13	9	1	35	66%	4,528
Racemic Epinephrine 2.25%							
½	5	4	2		11	55%	
1	7	3	1		11	36%	1,235
2	10	1			11	09%	999
24							302
Total	22	8	3		33	33%	2,536
Triethylene Glycol (100%)							
½	8	2	1		11	27%	
1	9	1	1		11	18%	911
2	10		1		11	09%	602
24							371
Total	27	3	3		33	18%	1,844
Chloresium (100%)							
½		4	5		9	100%	
1	6	2	1		9	33%	630
2	9				9	0%	282
24							73
Total	15	6	6		27	44%	985
Pantopaque							
½	7	1			8	12%	
1	8	1			9	11%	446
2	8	1			9	11%	573
24							317
Total	23	3			26	11%	1,336

* 0.04 unit or more.

powerful bronchodilator. One per cent neosynephrin and 2.5 per cent racemic epinephrine (Vaponefrin, analogous to 1.5 per cent U.S.P. epinephrine) were used as diluents. The effects on absorption of these two drugs as contrasted to saline were reflected in the blood levels (chart 2 and figure 1).

The *total percentage of positive sera* with saline (69 per cent) and neosynephrin (66 per cent) are essentially the same; whereas, only 33 per cent

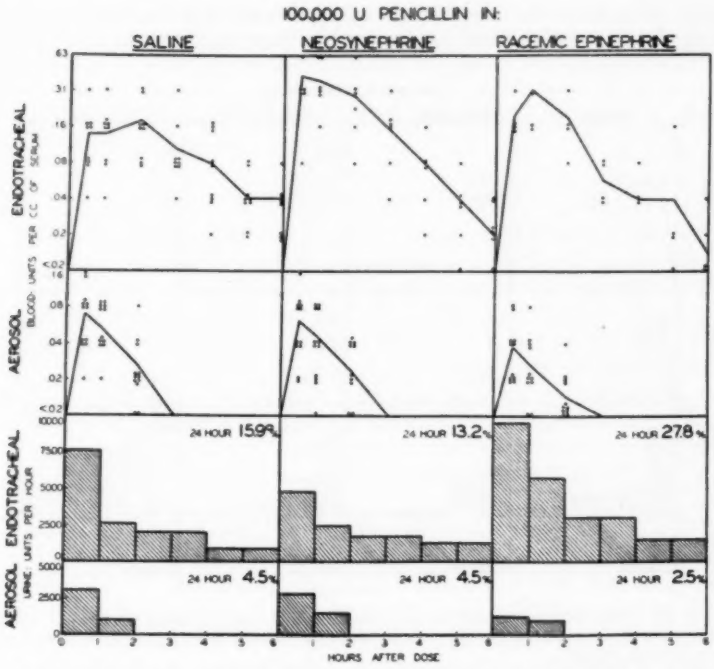

FIG. 1. Blood level curves and urinary excretion following the administration of 100,000 units of crystalline penicillin G potassium by intratracheal and aerosol routes of administration in various diluents.

positive sera were obtained with racemic epinephrine (chart 1). The differences in the *percentage of sera still positive at the end of two hours* demonstrate the vasoconstricting action of neosynephrin on the absorption of penicillin; 45 per cent of the two-hour sera were positive as compared to 25 per cent with saline and only 9 per cent with epinephrine. The *percentage of sera exceeding the minimum therapeutic level* follows much the same pattern: with saline, 39 per cent, with neosynephrin, 29 per cent; and with epinephrine, 9 per cent. Total urinary excretions were consistent with the blood

levels; epinephrine, which gave the lowest blood levels, also gave the lowest urinary excretion.

Triethylene glycol, Pantopaque and chlorophyll were chosen as diluents for various reasons. Glycol vapors have been employed for air disinfection for many years.[7, 8] Singer et al.[9] demonstrated the delaying action of propylene glycol on the absorption of injected penicillin. Chlorophyll (Chloresium) * was used in the form of a purified water-soluble derivative. It has been used extensively in the local treatment of traumatic and thermal wounds because of its deodorizing and antibacterial properties.[10, 11] The healing action of chlorophyll derivatives has been attributed to their glyco-

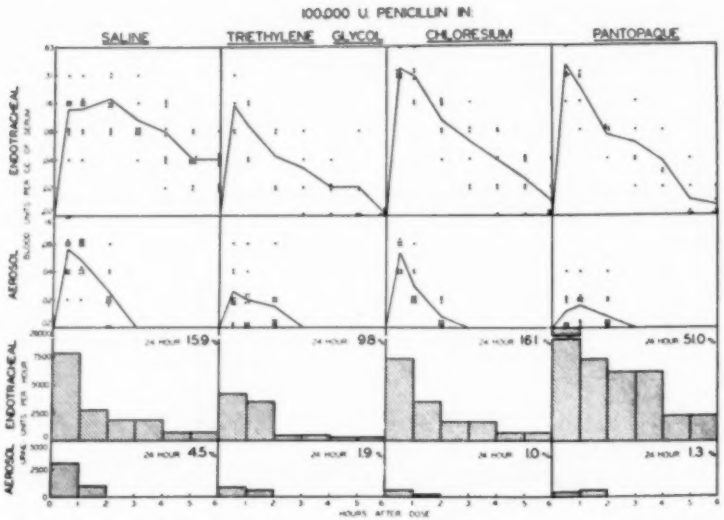

FIG. 2. Blood level curves and urinary excretion following the administration of 100,000 units of crystalline penicillin G potassium by intratracheal and aerosol routes of administration in various diluents.

lytic, oxygenating and other enzymic activities. We felt that such a substance might have a favorable action in suppurative disease of the lung. Its effect on penicillin absorption and excretion, when aerosolized as a diluent of the latter, was therefore investigated. Pantopaque, a mixture of ethyl esters of isomeric iodophenylundecylic acids, is an absorbable oil-type contrast medium of low viscosity, ordinarily used for myelography. Romansky [12] suggested a lipiodol-penicillin suspension for management of suppurative lung conditions. However, we felt that repeated injections of such a slowly eliminated, heavy oil would be undesirable in such diseases. A thinner, more easily eliminated iodized oil was considered more appro-

* Chloresium, Rystan Co.

priate for intrapulmonary use. Since triethylene glycol and Pantopaque are relatively viscid and not easily aerosolized by the conventional nebulizer, a special Vaponefrin nebulizer, dispensing a larger particle size, was used.

These diluents, whose effect on absorption and excretion of penicillin is of a chemical or mechanical action, have a marked effect on the serum levels (chart 2 and figure 2). The blood levels and total urinary excretion were consistently lower than those obtained with physiologic saline. The *total percentage of positive sera* (chart 1) using triethylene glycol (18 per cent) or Pantopaque (11 per cent) compare unfavorably with that of saline (69 per cent); chlorophyll produced a somewhat higher number of sera in the therapeutic range (44 per cent). The *percentage of sera positive at the end of two hours* and the *percentage of sera whose penicillin activity exceeded the minimum therapeutic level* also did not compare favorably to that of saline when these diluents were used.

Intratracheal Administration

Direct instillation into the trachea should yield accurate data on the manner in which diluents affect absorption of penicillin from the tracheobronchial tree. With aerosolization, losses occur at the apparatus, into the air and in the mouth. We have shown elsewhere that only 35 per cent of an aerosolized substance actually reaches the lung. Exact quantitative evaluation is therefore difficult. In contrast, no losses occur with intratracheal administration unless the injected substance causes enough chemical irritation to produce cough and expectoration in spite of topical anesthesia.

We, therefore, elected to inject directly into the trachea the same diluents previously used by the aerosol route. Penicillin assay of bloods and urines following this type of administration were tabulated (chart 3) and correlated with the aerosol data (figures 1 and 2).

The results following the use of neosynephrin, epinephrine and saline as penicillin vehicles, by both aerosol and intratracheal routes, are compared in figure 1. Neosynephrin 1:100 was used for aerosolization but was diluted to 1:1,000 for intratracheal injection; racemic epinephrine (analogous to 1.5 per cent U.S.P. epinephrine) was employed for inhalation; and epinephrine for direct instillation was diluted to a 1:10,000 concentration because marked side reactions occurred with higher concentrations. Despite such low dilutions, these substances exerted a profound effect on the blood levels and urinary excretion of penicillin when injected endotracheally.

Certain striking facts are partially obscured by the logarithmic ordinates of our graphs. Actually, the average blood level at one-half hour following neosynephrin (0.43 unit) was exactly three times that obtained when saline was the diluent (0.14 unit). The ratio was maintained fairly closely at one hour and less so at two hours; at four hours, the average levels were the same (0.08 unit). The neosynephrin curve remained within the therapeutic range for five hours; the saline curve remained so for six hours. The

CHART III

Blood Levels and Urinary Excretions of 100,000 Units of Crystalline Penicillin G Potassium (C.S.C.) in 10 c.c. of Various Diluents by Tracheal Catheter in Normal Males

	Blood							Urinary Excretion					
	½ hr.	1 hr.	2 hr.	3 hr.	4 hr.	5 hr.	6 hr.	1 hr.	2 hr.	4 hr.	6 hr.	24 hr.	Total
Physiologic Saline													
T. C.	.04	.04	.08	.08	.16	.04	.04	4,399	1,000	998	1,123	562	8,082
H. R.	.08	.08	.08	.08	.08	.08	.04	4,836	7,375	8,125	592	393	21,321
R. M.	.08	.16	.16	.08	.08	.08	.04	7,062	7,062	4.680	—	377	19,161
R. H.	.16	.08	.08	.08	.16	.04	.04	967	429	1,903	1,326	0	4,625
E. F.	.08	.16	.31	.31	.16	.04	.08	—	—	—	—	—	—
N. Mc.	.16	.16	.31	.04	.04	.02	.02	11,937	468	1,326	904	249	14,684
E. P.	.31	.31	.16	.16	.04	.04	.02	9,661	1,875	826	427	149	12,938
J. O.	.16	.16	.16	.08	.04	.04	.02	13,370	2,315	5,820	1,792	0	23,297
E. D.	.16	.16	.16	.08	.02	.02		12,000	1,250	5,250	4,650	200	23,350
Average	.14	.14	.17	.11	.08	.04	.04	7,654	2,597	3,866	1,546	241	15,932
Neosynephrin (1:1000)													
R. H.	.31	.31	.08	.04	.02	0	0	3,435	5,000	3,125	1,405	525	13,490
E. F.	.08	.16	.23	.16	.16	.08	.02	3,060	1,875	1,185	—	650	6,770
N. McL.	.31	.31	.31	.16	.08	.04	.04	2,500	312	624	10	0	3,446
E. P.	.31	.63	.31	.08	.08	.04	.04	—	2,250	6,250	2,500	187	—
J. O.	1.25	.63	.16	.16	.04	.02	.02	5,370	3,125	288	498	118	9,399
E. D.	.31	.31	.63	.31	.08	.04	.02	10,000	2,250	10,250	7,870	2,500	32,870
Average	.43	.39	.29	.15	.08	.05	.02	4,873	2,468	3,620	2,456	663	13,196
Epinephrine (1:10,000)													
J. O'D.	.16	.16	.16	.08	.08	.16	.04	1,638	9,500	7,500	6,562	2,250	27,450
J. S.	.31	.63	.08	.04	.04	0	0	13,500	2,375	3,876	515	6,825	27,091
T. A.	.16	.16	.31	.04	.02	.02	0	10,750	6,250	10,750	2,313	1,575	31,638
H. D.	.16	.31	.16	.08	.04	.02	.02	12,250	5,000	2,813	2,563	2,275	24,901
Average	.20	.32	.18	.06	.05	.05	.02	9,555	5,781	6,235	2,988	3,206	27,770
Triethylene Glycol (100%)													
E. F.	.08	.04	.02	.02	.02	.08	0	2,180	5,820	545	545	150	8,940
N. McL.	.31	.16	.08	.04	.02	0	0	3,040	5,060	900	530	120	9,650
E. P.	.16	.16	.08	.08	.04	.02	0	7,500	2,620	3,000	2,370	334	15,824
J. O.	.08	.04	.02	0	0	0	0	3,930	734	331	0	0	4,995
Average	.16	.10	.05	.04	.02	.02	0	4,162	3,559	1,189	861	151	9,852
Chloresium (100%)													
R. H.	.31	.31	.08	.02	0	0	0	15,000	6,860	5,310	1,150	50	28,370
N. McL.	.31	.16	.08	.04	.02	.02	.02	9,480	2,730	3,120	2,960	370	18,660
E. W.	.31	.31	.16	.08	.08	.04	0	2,620	625	4,620	2,090	140	10,095
E. P.	.31	.31	.16	.08	.04	.04	0	3,060	3,060	3,740	1,385	1,338	12,583
J. O.	.31	.16	.04	.02	.02	.02	0	6,570	2,805	1,482	2,340	140	13,337
E. D.	.63	.63	.16	.16	.08	.04	.04	6,500	4,370	2,500	0	0	13,370
Average	.36	.31	.11	.07	.04	.03	.01	7,205	3,408	3,462	1,654	340	16,069

CHART III—*Continued*

	Blood							Urinary Excretion					
	½ hr.	1 hr.	2 hr.	3 hr.	4 hr.	5 hr.	6 hr.	1 hr.	2 hr.	4 hr.	6 hr.	24 hr.	Total
Pantopaque													
P. M.	.63	.31	.08	.16	.08	.04	.02	33,250	8,500	17,500	15,375	89	74,714
P. F.	.31	.31	.08	.04	.03	.02	.01	27,000	10,500	16,500	402	200	54,602
A. H.	.16	.08	.04	.02	—	0	0	—	—	—	—	—	—
J. F.	.31	.16	.08	.04	.02	0	0	33,750	5,000	8,375	2,122	162	49,409
J. O'D.	.31	.31	.08	.08	.03	0	0	12,500	4,992	6,718	800	200	25,210
Average	.34	.23	.07	.07	.04	.01	.01	26,625	7,248	12,273	4,675	162	50,983
Human Serum													
J. C.	.23	.08	.08	.04	.02	0	0	4,000	4,000	2,500	2,500	115	12,115
R. C.	.16	.16	.16	.08	.02	.02	0	6,240	6,240	12,500	12,500	438	37,918
R. W.	.16	.08	.08	.06	.06	.04	.04	12,500	12,500	12,500	6,240	1,575	45,315
J. H.	.31	.63	.31	.31	.16	.08	.04	18,740	25,000	12,500	1,560	2,850	60,650
Average	.22	.24	.16	.12	.07	.04	.02	10,370	11,935	10,000	5,700	1,245	39,250

penicillin blood curve with endotracheal epinephrine lay between the neosynephrin and saline curves and remained within the therapeutic range for five hours.

The amount of penicillin excreted in the urine following endotracheal administration with these diluents varied. Average recovery in the urine after the use of epinephrine was greater at each time interval than with either neosynephrin or saline and the total average excretion was approximately twice that obtained with either of the other vehicles. Although the total average excretion with neosynephrin was slightly lower than with saline, most of this difference occurred in the first hour; after the fourth hour, recovery with neosynephrine was moderately higher than with saline.

The blood level curves following aerosolization of penicillin in each of these diluents have been fully discussed above. Correlation with the endotracheal data just presented discloses fair consistency. However, the lower recovery in the urine following aerosolization with epinephrine is inconsistent with the comparatively high recovery following intratracheal injection with this same substance.

The absorption and excretion of penicillin when injected endotracheally with triethylene glycol, chlorophyll or Pantopaque is compared to saline (figure 2). A micronized crystalline penicillin G potassium powder with an average particle size of less than two micra was mixed with Pantopaque when this substance was studied intratracheally. Unlike all other substances which we injected into the trachea, chlorophyll and especially triethylene glycol were markedly irritating in 100 per cent concentrations and varying amounts of penicillin were lost because of resultant cough and expectoration. It is noteworthy that instillation of Pantopaque did not lead to cough.

The penicillin blood level curve with endotracheal triethylene glycol is generally lower than the saline curve. A rapid falling off was noticeable from the first hour and the average level was maintained at the minimum therapeutic level for only four hours. Part of this was due to the loss of penicillin incurred following the cough and expectoration produced by chemical irritation.

The penicillin blood levels with endotracheal chlorophyll were more than twice as high as those with saline at the end of one-half and one hour following injection. A very rapid decline occurred thereafter and it was impossible to maintain levels within a therapeutically effective range after four hours. Because 100 per cent Chloresium was irritating to the anesthetized tracheobronchial tree, a 25 per cent dilution was given to two subjects. Cough did not occur. The blood level curve (not illustrated) was appreciably lower and failed to stay in a therapeutic range after three hours; recovery in the urine was also proportionately lower.

Endotracheal penicillin in Pantopaque gave blood levels similar to those observed with chlorophyll. The one-half and one hour levels following injection were higher than corresponding levels with saline and the curve fell below the minimum therapeutic range after four hours.

The recovery of penicillin in the urine following triethylene glycol and chlorophyll was consistent with the respective blood level curves. Total and fractional excretions showed patterns similar to saline. Such was not the case with Pantopaque, for more than 50 per cent was recovered (one-half of this during the first hour). This striking excretion is not easily correlated with the absorption curve.

The blood level curves following aerosolization of penicillin in each of these diluents have been previously discussed. The chlorophyll curve most closely resembles the saline curve, but it declines rapidly. The markedly inferior curves with glycol and Pantopaque are probably traceable to the increased viscosity of these substances necessitating the use of a large particle size nebulizer with a consequent smaller number of particles reaching the absorptive areas of the lung. Recovery in the urine was extremely low with each diluent.

Interest in the effect of human serum on the absorption of crystalline penicillin from the lung was stimulated by the fact that protein molecules are too large to be readily absorbed through the alveolar barrier. If penicillin formed a stable combination with such large molecules, high local concentrations and very low blood levels would be expected. Courtice and Phipps,[13] during the course of phosgene poisoning studies, showed that serum is very slowly absorbed from the lung. Drinker [14] similarly injected crystalline egg albumin, serum and various other substances of large molecular weight intratracheally and was unable to recover more than traces from either the blood or the cannulated right lymphatic duct. On the other hand, T–1824 (Evans blue), a dye which combines with the protein molecule, was promptly recovered from blood and lymph when it was injected

or aerosolized in a watery solution. However, only traces of this dye were detectable when it was injected intratracheally with protein. Ingraham and one of the authors [15] (E.A.G.) similarly attempted to slow down absorption of penicillin from muscle. The amorphous penicillin available at that time was assayed and injected intramuscularly in saline or in solution with 250 mg. gamma globulin or 250 mg. fraction V albumin. Blood samples were then taken every 15 minutes and assayed for penicillin activity by the present method. The serum level curves in all three instances were almost identical (figure 3). Absorption from muscular tissue could not

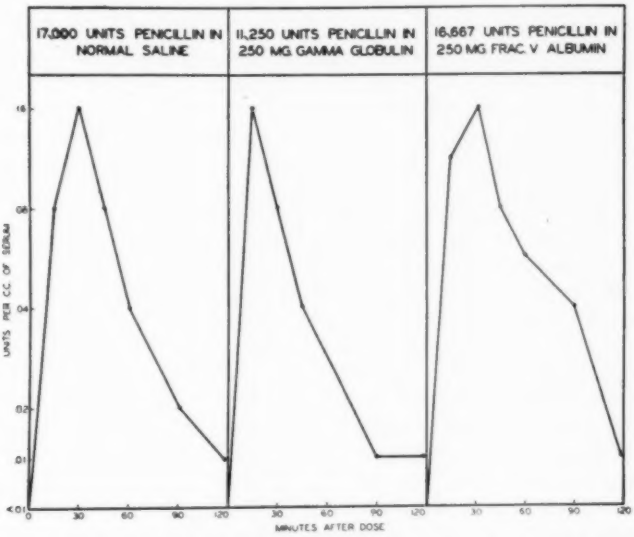

FIG. 3. Blood level curves following the administration of amorphous penicillin in normal saline, gamma globulin and fraction V albumin.

be retarded, therefore, by this method. Tompsett et al.[16] have demonstrated that in a state of equilibrium 60 per cent of crystalline penicillin G combines with serum protein, specifically the V fraction albumin, and that this albumin-penicillin is inactive. Since the combination is an equilibrium reaction, penicillin was liberated as rapidly from its protein bond as the free portion was eliminated. Absorption, therefore, was not delayed. Since absorption from the alveoli proceeds much more slowly, an appreciable delay might possibly be detected if the protein-penicillin mixture were administered intratracheally. The blood levels obtained (chart 3) were higher at the early intervals, but, in general, they approximated the levels with physiologic saline more closely than with any of the other diluents. The drop below minimum therapeutic activity at six hours indicates that human

serum is not effective as a depot for penicillin. The average recovery of 39,250 units in the urine (chart 3) was comparatively high.

Discussion

The effect of several diluents on the absorption of penicillin from the lung has been studied by aerosol and intratracheal routes of administration. Bloods and urines were assayed for penicillin activity and the results compared to those obtained following the administration of penicillin in saline via the same routes.

Penicillin in 10 c.c. neosynephrin (1:1000) by intratracheal injection gave initial levels three times as high as corresponding levels with saline. In addition to these initially high levels, a therapeutic blood level was maintained for five hours. The accepted bronchovasoconstrictor action of this drug should tend, theoretically, to slow down adsorption into the blood stream rather than hasten it. The results with aerosol penicillin-neosynephrin closely resembled those with aerosol penicillin-saline; a greater percentage of positive sera at the end of two hours with aerosolized neosynephrin demonstrated delayed absorption. Neosynephrin aerosol appeared to produce a more uniform and diffuse shrinkage of the bronchial mucous membrane than when administered by the intratracheal route. Neosynephrin, as a bronchovasoconstrictor, afforded marked symptomatic relief when obstruction of the bronchi was due to swollen, edematous mucous membrane. It is more stable than epinephrine, and its sympathicomimetic effects, which are slower in onset but more lasting, are attended with less untoward reactions. Furthermore, its tendency to retard the absorption of aerosolized penicillin, thereby aiding greater local concentrations, is highly desirable.

Epinephrine is more potent as a bronchodilator than as a bronchovasoconstrictor. When this drug was injected intratracheally in a 1:10,000 dilution with penicillin, the blood level curve lay between the saline and neosynephrin curve. The blood levels remained therapeutically effective for five hours. The much higher fractional and total recovery of penicillin in the urine than that obtained with either neosynephrin or saline was striking. When aerosolized with penicillin, the blood levels and recovery in the urine were less than those obtained with either neosynephrin or saline. The vasoconstrictor action of epinephrine, however, was still in evidence. Since epinephrine primarily constricts arterioles rather than capillaries, such low blood levels might indicate that normally the arterioles are an important route of absorption. The comparatively high urinary excretion, however, does not bear this out; a delayed absorption would be reflected in a lower excretion inasmuch as the body inactivation or detoxification of penicillin would have more time to progress.

Side effects, including cough, were notably absent when neosynephrin and epinephrine, in the described dosages, were aerosolized or injected intratracheally. There did not appear to be any contraindication to their com-

bination with penicillin when the clinical picture warranted the use of either to combat bronchospasm, mucosal swelling or both. On the contrary, definite beneficial local effects, in addition to their pharmacologic actions, appeared to be exerted.

Triethylene glycol did not seem to hold any particular advantage as a diluent by either the aerosol or intratracheal routes. As it was too viscid for easy aerosolization with the conventional nebulizer, the blood levels following its administration with a special large particle size nebulizer were disappointing. Moreover, by intratracheal route, it was extremely irritating to the tracheobronchial tree. Low blood levels and urinary excretion may be argued as indicating local retention in the lung; in fact, studies in which triethylene glycol was tagged with radioactive substances indicated a greater local retention of penicillin when combined with this diluent than with other substances.[17] A slowing of absorption would, of course, result in low early blood levels but, conversely, blood samples at later intervals would continue to show penicillin activity, albeit still in the lower ranges. Following intratracheal injection, all individual six-hour levels and one-half of the five-hour levels were zero. Following aerosolization, only one of the 11 sera tested at the end of two hours was within a therapeutic range. With neither route, therefore, could delayed absorption be ascribed to a glycol-penicillin combination. Other reports have described the glycols as enhancing the bactericidal action of penicillin when combined with the latter. In fact, a bactericidal action of glycol alone in the blood stream has been claimed.[18] However, these conclusions were based on a bacteriological technic which used *B. subtilis* as a test organism; normal blood has been shown to exhibit antibodies in various titers for these organisms.[19] A false impression of bactericidal activity in the serum may, therefore, result when *B. subtilis* is used as the test organism. In addition to our routine studies, we repeated the above mentioned study [18] where 100,000 units of penicillin was aerosolized in a mixture of 19 c.c. of triethylene glycol and 1 c.c. of glycerol. We employed the O.E.M. head-tent. A double assay of several blood and urine specimens was done using both streptococcus No. 98 and *B. subtilis* as test organisms. As we could not demonstrate any penicillin in either the blood or urine, we were, therefore, unable to detect either delay in absorption or potentiation of the bactericidal action of penicillin when it was combined with glycol.

Initial blood levels, with chlorophyll as a diluent, were higher than the saline levels, especially when administered intratracheally. With both routes, however, levels were not maintained within a therapeutic range for as long a time as with saline. Chlorophyll, in 25 per cent dilution, was not irritating to the tracheobronchial tree but full strength solution, when given intratracheally, did cause cough despite topical anesthesia. However, chlorophyll may be of practical value when the bacterial flora includes anaerobic organisms. Because it causes more rapid absorption of penicillin, its administration would have to be repeated at shorter time intervals.

In a previous study,[1] it was pointed out that routine intratracheal administration of penicillin was usually not practical for several reasons. At the same time, it was felt that this method of treatment could be utilized in conjunction with bronchoscopy, bronchography and other procedures requiring endotracheal instillation. Therefore, the effect of iodized oil on penicillin absorption was of great interest. Pantopaque is much less viscid than lipiodol or iodochlorol. It was used because of certain practical considerations which favor its clinical use in place of the heavier, more difficultly eliminated oils. It was felt that a light oil such as Pantopaque would still be heavy enough to sterilize or cleanse cylindrical and saccular dilatations of the bronchi which have become clogged with thick mucus. Its greater specific gravity would encourage a "floating" or displacement of such plugs which could then be more easily expectorated. Combining penicillin with a physical therapeutic agent of this type would probably be advantageous. Since the iodine of Pantopaque (approximately 30 per cent) is present in firm organic combination, it was not to be expected that the iodine present would act as an expectorant. However, some loosening of the secretions may occur. The blood level curve with intratracheal Pantopaque was maintained in the therapeutic range for four hours. In comparison to every other diluent studied, the urinary excretion of more than 50 per cent was astounding. Since both the diluent (Pantopaque) and the penicillin preparation (micronized powder) were different from the other substances studied via the same route, some factor, either in the combination or in either of the individual substances, could possibly be the cause of this unusual recovery in the urine. Unlike other diluents which formed a true solution, penicillin powder was merely suspended in Pantopaque. Further studies are planned with micronized penicillin by this and the aerosol route and also with radiopaque substances by the intratracheal route.

Localization of both penicillin G and K has been demonstrated in the kidney, lung and liver to an extent not explained by the blood or extracellular fluid content of these organs.[20] Penicillin G is localized more extensively in the lung and kidney; penicillin K, more extensively in the liver. Pantopaque, human serum and epinephrine may possibly enhance this natural localization of penicillin G in the lung and kidney. This mechanism may offer a possible explanation for the markedly higher urinary excretion with average or below average blood level curves obtained with these diluents when injected endotracheally.

Summary

1. The effect of several diluents on the absorption of penicillin from the lungs has been studied by aerosol and intratracheal routes of administration. Assay of penicillin activity in the serum and recovery in the urine was compared to results obtained following the administration of penicillin in saline by the same routes.

2. Both neosynephrin and epinephrine, constrictors of the bronchial mucous membrane, caused higher initial blood levels than corresponding results with saline when injected intratracheally. Levels were sustained within a therapeutic range for five hours. The bronchovasoconstricting action of neosynephrin was more in evidence when aerosolized with penicillin.

3. When the aerosolization of either or both of these substances with penicillin was indicated clinically, their local pharmacologic action on the tracheobronchial tree favorably affected absorption of penicillin. Irritation or side reactions were not present with either route of administration.

4. Triethylene glycol was too viscid for easy aerosolization and too irritating, at full strength, for intratracheal injection. Neither a bactericidal action of its own, enhancement of penicillin activity in the serum nor a delaying action on the absorption of penicillin could be demonstrated.

5. Chlorophyll caused more rapid absorption of penicillin but levels were not maintained within a therapeutic range for as great a length of time as with saline. One hundred per cent solution was irritating to the tracheobronchial tree, but a 25 per cent solution was well tolerated by intratracheal instillation. Chlorophyll with penicillin, in the treatment of mixed gram positive and negative bacterial flora, should be repeated frequently in order to maintain high local antibiotic activity. Chlorophyll (endotracheal) should be of definite value for the management of anaerobic bacterial bronchopulmonary infections.

6. Intratracheal injection of emulsions of penicillin in the lighter iodized oils in the treatment of bronchopulmonary suppurative disease is discussed. The cleansing action of the oil at the site of localized collections of pus and the displacement or "floating" of mucous plugs would permit more effective local action of penicillin injected at the same time.

7. Human serum as a vehicle did not greatly alter the absorption of penicillin from the lung.

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TREATMENT OF HEART AND KIDNEY DISEASE AND OF HYPERTENSIVE AND ARTERIOSCLEROTIC VASCULAR DISEASE WITH THE RICE DIET*

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THE treatment of heart and kidney disease and of hypertensive and arteriosclerotic vascular disease with the rice diet is either ineffective or dangerous, unless it is done under rigidly controlled conditions. Ineffective, because small or "minimal" additions to the diet may spoil the entire therapeutic result; dangerous, because a strict observance of the diet may lead to a deficiency of vitally important elements unless care is taken that the equilibrium between intake and loss of these substances is maintained. For both reasons, therefore, continuous supervision, over a long period of time, including constant checks of blood and urine chemistry, is essential.

Rigidly controlled conditions are likewise indispensable for the evaluation of the therapeutic results. Claims of positive or negative results based on nothing but blood pressure readings for four to eight weeks before and after treatment and not substantiated by heart films, electrocardiograms, eye-ground photographs and chemical findings do not contribute much to the solution of this problem.

The same authors who a few years ago insisted that the restriction of salt, protein or fat is unwarranted in the treatment of hypertensive and arteriosclerotic vascular disease, now admit the importance of these dietary restrictions. No matter what the value of the restriction of sodium or of chloride or of protein or of cholesterol may be, the fact is: The rice diet contains less sodium and less chloride than any other diet which has been devised to reduce the sodium and chloride intake. It contains less protein than any other diet which has been devised to reduce the protein intake. It contains less cholesterol and other fat than any other diet which has been devised to reduce the cholesterol and fat intake.

The rice diet contains in 2,000 calories less than 5 gm. of fat and about 20 gm. of protein derived from rice and fruit and less than 200 mg. of chloride and 150 mg. of sodium. This does not mean that the patient's caloric intake is restricted to 2,000 calories; it varies according to whether weight gain or weight loss, protein increase or protein decrease is desirable in the individual patient.

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Figure 1 shows a comparison of the most important constituents of the urine on a normal diet and after at least two months on the rice diet. The total nitrogen content has decreased from 15.0 gm. to 2.3 gm.; the urea nitrogen from 12.0 gm. to 1.1 gm.; the uric acid nitrogen from 0.3 gm. to 0.08 gm.; the total creatine nitrogen from 0.6 gm. to 0.4 gm.; the ammonia nitrogen from 0.6 gm. to 0.1 gm.; the sodium from 4.0 gm. to 0.01 gm. The potassium has increased from 2.0 gm. to 3.0 gm. The chloride has decreased from 7.0 gm. to 0.1 gm.; the inorganic phosphate from 1.0 gm.

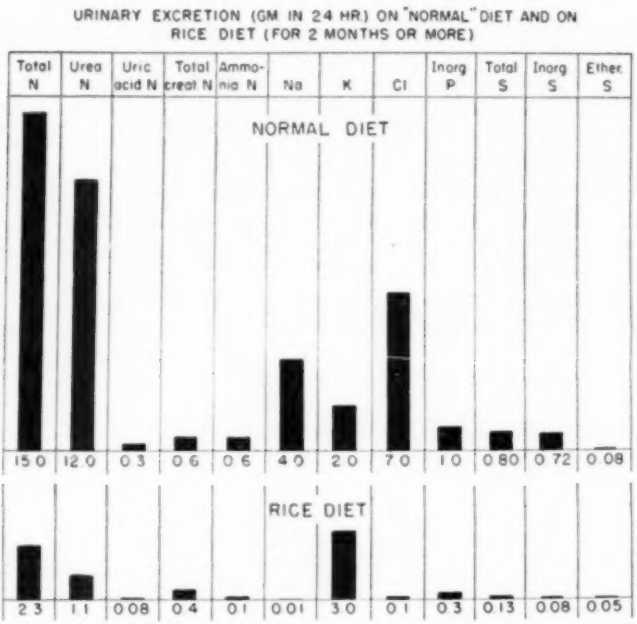

FIG. 1.

to 0.3 gm.; the total sulfate from 0.80 gm. to 0.13 gm.; the inorganic sulfate from 0.72 gm. to 0.08 gm.; the ethereal sulfate from 0.08 gm. to 0.05 gm.

The figures show that the marked decrease in the intake of nitrogen, sodium, chloride, sulfate, etc., on the strict rice diet, is followed by a marked decrease in the excretion of these substances by the kidney. Any deviation from these figures—except in rare cases—indicates that this particular diet has not been followed strictly for any length of time, and also in what way—either deliberately or unintentionally—it has been changed.

A small amount of nitrogen is also excreted through the bowels; a comparison of the daily nitrogen intake with the daily nitrogen output by stool

and urine shows that the nitrogen equilibrium on the rice diet can easily be maintained (table 1).

There are other indications that, because of the protein sparing action of the carbohydrates, the protein part of the rice diet is adequate and that there is no lack of essential amino acids; e.g., the fact that the production of hemoglobin is normal and that anemia does not develop. Also the fact that blood urea and non-protein nitrogen decrease on the rice diet whereas in starvation and in protein deficiency the body uses its own protein and the non-protein nitrogen and the urea nitrogen in the blood increase.

Other differences between starvation and the rice diet are: in starvation, the serum calcium is decreased, on the rice diet unchanged. In starvation, the plasma protein and the A/G ratio are decreased, on the rice diet unchanged or, if low before, often become normal. In starvation, the blood sugar is decreased, on the rice diet unchanged. In starvation, the carbohydrate tolerance is decreased, on the rice diet increased. In starvation, the serum phospholipids are increased, on the rice diet decreased. In starvation, the CO_2 combining power is decreased, on the rice diet increased. In starvation, the blood volume remains unchanged or—in relation to body weight—increases; on the rice diet, according to Murphy's determinations, it decreases. In starvation, the interstitial fluid remains unchanged or increases; on the rice diet it decreases. (N. B., there is no simple relationship between volume changes and clinical course.) In starvation, the excretion of total creatine bodies in the urine is unchanged; on the rice diet it is decreased. In starvation, the excretion of creatine, ammonia and organic acids is increased, on the rice diet decreased. In starvation, the excretion of total sulfate and inorganic phosphate is decreased, on the rice diet markedly decreased (table 2).

TABLE I

Nitrogen Balance After 60 Days on Rice Diet, gm.N in 24 hrs.
(Averages of 4 consecutive days)

	Intake	Output	Balance
		urine 2.61 stool 1.81	
W. C.			
m., 59	4.66	4.42	+0.24

In 490 patients with hypertensive vascular disease and an initial non-protein nitrogen of 20 to 45 mg. per 100 c.c. of blood, there was an average decrease of the non-protein nitrogen from 33 to 28 mg. per 100 c.c. of blood after an average period of 98 days. There was an average decrease of the urea nitrogen from 14 to 8 mg. (table 3). These figures are also interesting in another connection: a decreased salt intake in the diet with ensuing hypochloremia is usually followed by an increase in the blood urea nitrogen,

TABLE II

Chemical Differences between Starvation and Rice Diet

	Starvation	Rice Diet
Blood (or serum)		
Hemoglobin, RBC	Decreased	Unchanged
Calcium	Decreased	Unchanged
Total protein	Decreased	Unchanged (returned to normal if decreased before)
A:G ratio	Decreased	Unchanged
NPN	Increased	Decreased
Urea N	Increased	Decreased
Sugar	Decreased	Unchanged
Carbohydrate tolerance	Decreased	Increased
Phospholipid	Increased	Decreased
Alkali Reserve	Decreased	Increased
Blood volume	Unchanged	Decreased
Interstitial fluid	Unchanged or increased	Decreased
Nitrogen balance	Negative	In equilibrium
Urine		
Total nitrogen	Decreased	Markedly decreased
Urea N	Decreased	Markedly decreased
Creatinine + creatine	Unchanged	Decreased
Creatine	Increased	Decreased
Ammonia N	Increased	Decreased
Organic acids	Increased	Decreased
Total sulfate	Decreased	Markedly decreased
Inorganic phosphate	Decreased	Markedly decreased

and consequently by an increase in the total non-protein nitrogen. On the rice diet the salt *is* limited and the serum chlorides do decrease to a lower level. However, the restriction of the protein in the diet outweighs the effect of salt restriction and usually protects against the azotemia.

It might, perhaps, be well to talk less about the quantity of protein. The important thing is not how much protein is eaten, but how much of what kind of protein. There is actually no such thing as "protein." Proteins differ from each other in regard both to the type and the relative proportions of the various amino acids of which they are composed. They also differ in regard to rate and degree of assimilation. These differences as far as the patient is concerned are indicated by what is termed the biological value of

TABLE III

Average NPN and Urea-N of 490 Patients with Hypertensive Vascular Disease
(Initial NPN 20 to 45 mg. per 100 c.c. Blood)

	Before	After 98 (Average) Days of
	Rice Diet	
NPN (mg./100 c.c. Blood)	33	28
Urea-N (mg./100 c.c. Blood)	14	8

various proteins. It is of no advantage to the patient to receive a large amount of protein with a low biological value which cannot be properly utilized. Moreover, certain patients should use protein only for essential purposes and not merely to supply calories which can just as well be supplied by the oxidation and fermentation of carbohydrates.

The same considerations which apply to protein and essential amino acids are also valid with regard to fat and essential fatty acids. The absolute fat content of rice for instance is small, but the proportion of linoleic acid, an essential fatty acid, is high.

One of the lipids which is supposed to have an important rôle in the development of vascular disease is cholesterol. A high cholesterol concentration in the serum is frequently found in arteriosclerosis, coronary artery disease, exudative vascular retinopathy, hypertensive vascular disease, as well as in diseases of the lens and vitreous body, in uncontrolled diabetes mellitus and in the nephrotic stage of nephritis.

TABLE IV

Total Serum Cholesterol of 511 Patients with Hypertensive Vascular Disease

	Before Rice Diet	After Rice Diet	Average Period of Rice Diet (Days)
148 Patients with initial concentration below 220 mg. per 100 c.c. serum	186	171	120
363 Patients with initial concentration above 219 mg. per 100 c.c. serum	279	205	102

An easy way to produce arteriosclerosis is by feeding cholesterol to rabbits. In dogs it is not so easy. The aging process in the human species seems to be a change from the dog state to the rabbit state. The cholesterol metabolism becomes inadequate and the average serum cholesterol concentration of men of 50 is higher than that of men of 20 who have an identical cholesterol intake. However, if a 20 year old man has a disease which causes a hypercholesterolemia, the same sequelae may occur as in the 50 year old man. The literature describes cases of arteriosclerosis in diabetic children as young as one year.

We have examined the effect of the rice diet on the total serum cholesterol of 511 patients with hypertensive vascular disease (table 4). In 148 patients (29 per cent) who started the rice diet with a normal serum cholesterol, the average decrease was 15 mg. per 100 c.c. of serum after an average period of 120 days. In 363 patients (71 per cent) who had a hypercholesterolemia before the rice diet, the average decrease was 74 mg. after an average period of 102 days.

These figures show that, no matter from what fatty or non-fatty substances the cholesterol in the body is derived, and by what mechanism a high

TABLE V

Total and Free Cholesterol in Serum of 118 Patients with Hypertensive Vascular Disease (Initial total cholesterol 220–463 mg. in 100 c.c. serum)

	Before	After 56 Days (Average) on
	Rice Diet	
Total cholesterol (mg. in 100 c.c. serum)	288	217
Free cholesterol (mg. in 100 c.c. serum)	82.2	65.7
Ratio Free: Total cholesterol (%)	27.8	30.5

serum cholesterol concentration is produced, the serum cholesterol need not necessarily remain high, as has been assumed, but can be decreased by the rice diet.

As Starke has found, both cholesterol fractions, the free and the esterified cholesterol, decrease on the rice diet (table 5). One hundred and eighteen patients with an initial hypercholesterolemia of 220 to 463 mg. per 100 c.c. of serum were examined. The total cholesterol decreased in 113 of the 118 patients. The total cholesterol did not decrease in five of the 118 patients. In the entire group of 118 patients, there was a decrease of the total cholesterol from 288 to 217 (average), of the free cholesterol from 82.2 to 65.7 (average), of the esterified cholesterol from 205.8 to 151.3 (average). In

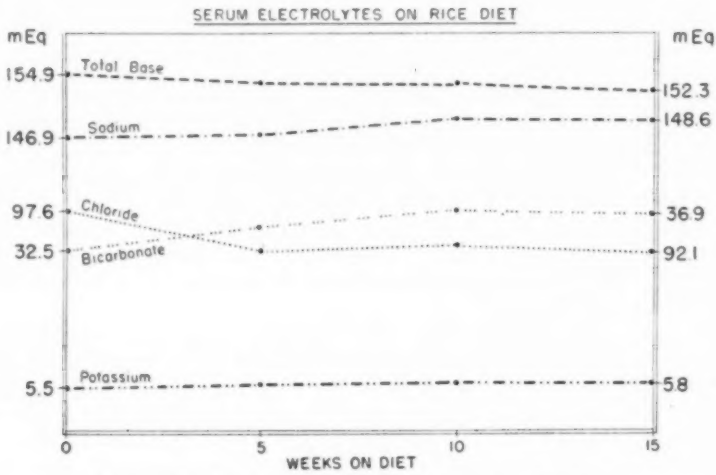

FIG. 2.

TABLE VI

Lipid Phosphorus in Serum of 42 Patients with Hypertensive Vascular Disease
(Mg. lipid P in 100 c.c. serum)

Before	After 78 Days (Average) on
	Rice Diet
9.91	8.87

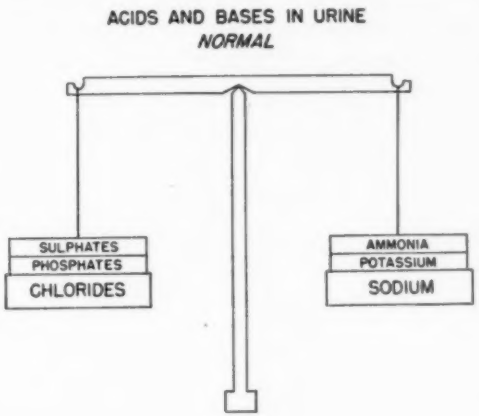

FIG. 3.

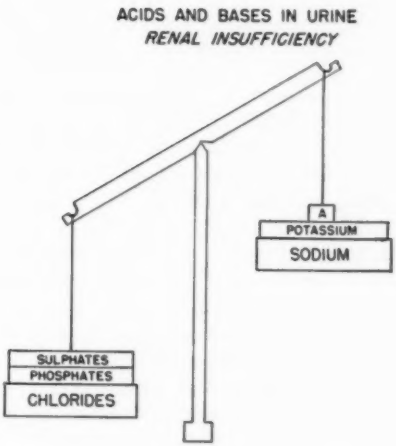

FIG. 4.

42 patients with hypertensive vascular disease, the serum phospholipids were determined. There was a decrease from 9.9 to 8.9 mg. lipid phosphorus per 100 c.c. (table 6).

Figure 2 shows the changes in concentration of sodium, chloride, potassium, bicarbonate, and total base in the serum of 12 patients on the rice diet. After an average period of 15 weeks, the serum chloride showed a definite decrease, the serum bicarbonate a definite increase; the serum sodium, potassium and total base remained relatively constant.

Another change in the mineral metabolism of patients on the rice diet is in the urinary excretion of inorganic sulfates and inorganic phosphates. The inorganic sulfate excretion decreases by 82 per cent, the inorganic phosphate excretion decreases by 62 per cent.

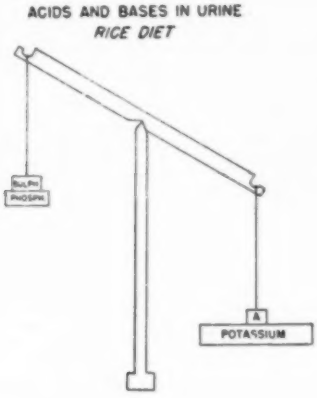

FIG. 5.

These findings are interesting for two reasons: Since phosphates and sulfates are derived mostly from protein, the decreased excretion of phosphorus and sulfur shows again that on the rice diet no endogenous protein is being broken down. Secondly, the sulfate and phosphate metabolism is important because of the acid-base balance. The scales (figure 3) represent this balance in the normal urine. The acids are on one side, the bases on the other side. In kidney insufficiency, the scale goes down on the acid side (figure 4). The kidney has lost one of its main metabolic functions: It is no longer able to form ammonia. On the rice diet, the urine chloride concentration is decreased. This does not affect the acid-base equilibrium because it is counterbalanced by the decrease in the sodium excretion. However, the potassium concentration on the base side is increased, and the sulfate and phosphate concentration on the acid side is decreased, so that even with an insufficient ammonia formation the urine becomes alkaline (figure 5).

Now let me turn from the chemical changes to the clinical changes produced by the rice diet. I will avoid long-winded statistics as much as possible and will try to discuss the main problems by showing you some typical cases as examples of what can be achieved in the individual patient.

The first case is that of a 13 year old school girl in the nephrotic stage of chronic nephritis. It is an example of the disappearance of marked generalized *renal* edema and hypoproteinemia on the rice diet. Early in Jan-

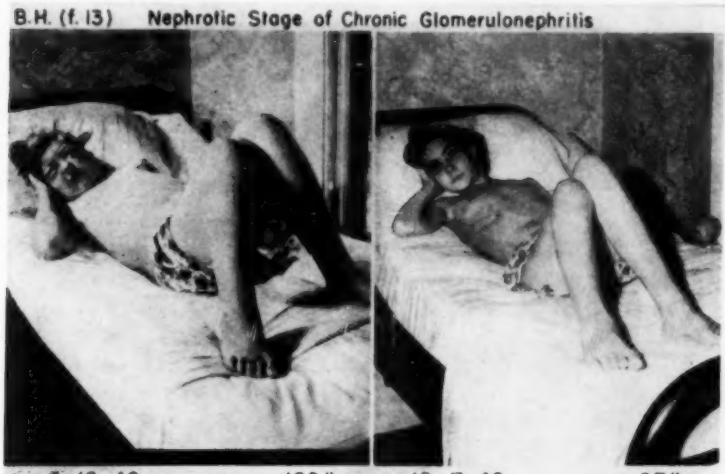

FIG. 6.

uary, 1948, this girl developed swelling of the lower extremities after a sore throat. She was treated by bed rest, salt-poor diet (for part of the time, high protein diet), and penicillin. In February, 1948, massive anasarca developed; a paracentesis was done which resulted in a weight loss of 22 pounds. Later, because of marked dyspnea, a thoracocentesis was necessary and one quart of fluid was removed from the right pleural cavity. During June, the facial edema which had been present since January became worse and the general edema and ascites increased. When the oliguria became serious, the patient was referred to us. The rice diet was started on June 18, 1948. No further paracentesis or thoracocentesis was done. The albuminuria decreased from 10.1 gm. per liter (average during the first 20 days on the rice diet) to 0.17 gm. (average after 111 to 131 days of rice diet). The

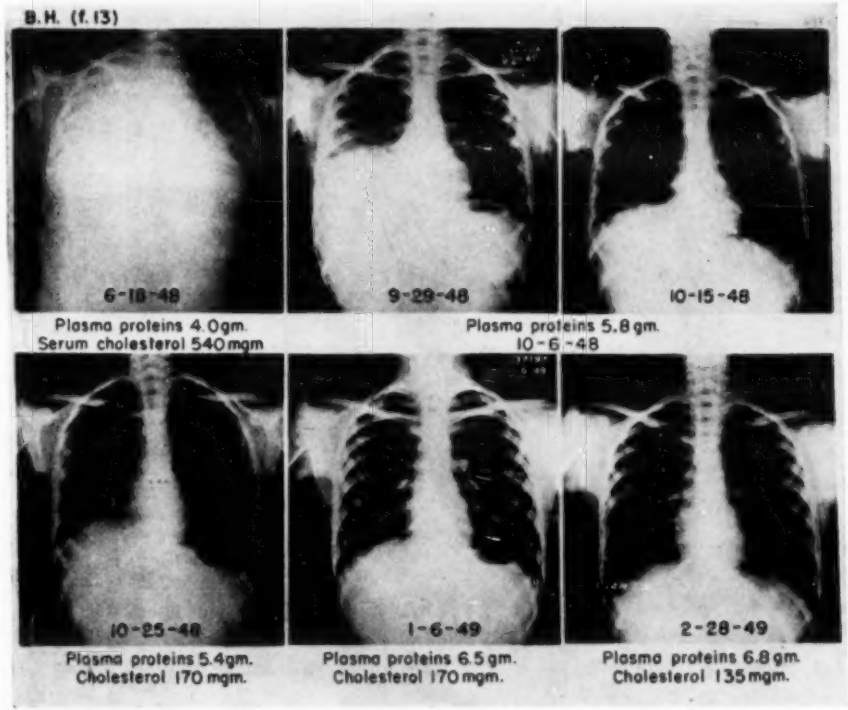
B.H. (f. 13)
6-18-48
9-29-48
10-15-48
Plasma proteins 4.0gm.
Serum cholesterol 540mgm
Plasma proteins 5.8 gm.
10-6-48
10-25-48
1-6-49
2-28-49
Plasma proteins 5.4gm.
Cholesterol 170 mgm.
Plasma proteins 6.5 gm.
Cholesterol 170 mgm.
Plasma proteins 6.8 gm.
Cholesterol 135 mgm.

FIG. 7.

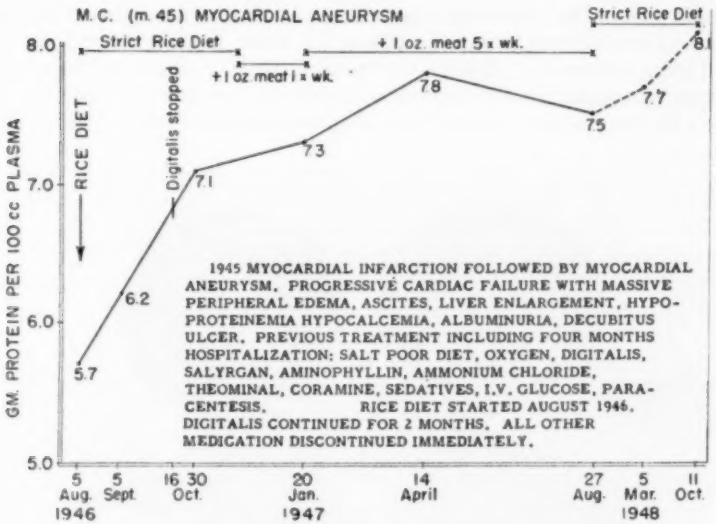

FIG. 8.

plasma protein increased from 4.0 gm. to 5.8 gm. The cholesterol decreased during this period from 540 mg. per 100 c.c. of serum to 185 mg. There was a total weight loss of 63 pounds in 15 weeks with gradual disappearance of ascites and pleural effusion. After eight months on the rice diet, the

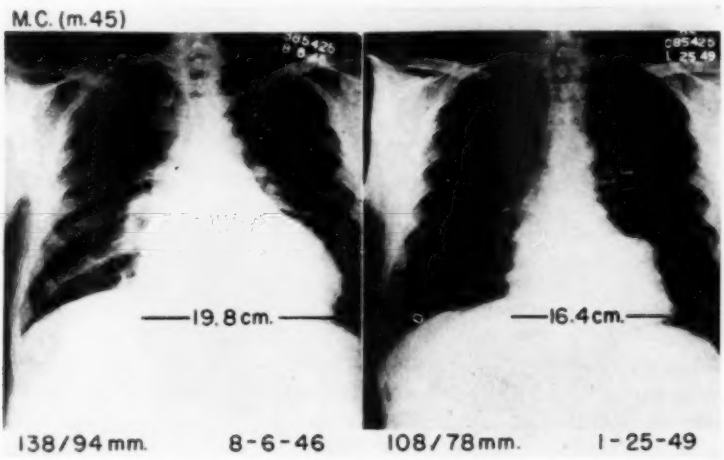

FIG. 9.

plasma protein had increased from 4.0 to 6.8 gm., the cholesterol had decreased from 540 to 135 mg. per 100 c.c. of serum (figures 6 and 7).

Figure 8 shows an example of the effect of the rice diet on the plasma protein of a patient with massive *cardiac* edema and ascites. This patient was a 45 year old man who had had a myocardial infarction in 1945. This

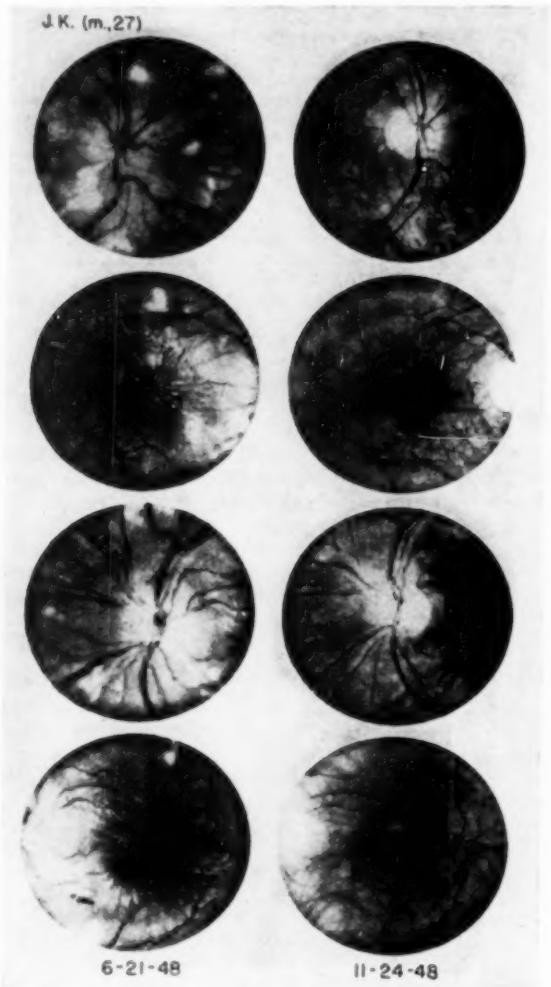

FIG. 10.

was followed by a myocardial aneurysm, progressive cardiac failure with massive peripheral edema, ascites, liver enlargement, hypoproteinemia, hypocalcemia, albuminuria, and decubitus ulcers. Previous treatment, including four months' hospitalization, consisted of salt-free diet, oxygen, digitalis, salyrgan, aminophyllin, ammonium chloride, theominal, coramine, sedatives; i.v. glucose; paracentesis. The rice diet was started August 7, 1946, and was strictly followed; a paracentesis was done August 13. Digitalis was continued for two months, but all other medications were discontinued immediately. There was a loss of weight (edema) of 50 pounds in 10 weeks. Up to the present time (two and one-half years later), the patient has received no medication; he is up and around and completely asymptomatic. The plasma proteins have increased from 5.7 gm. per 100 c.c. to 8.2 gm.

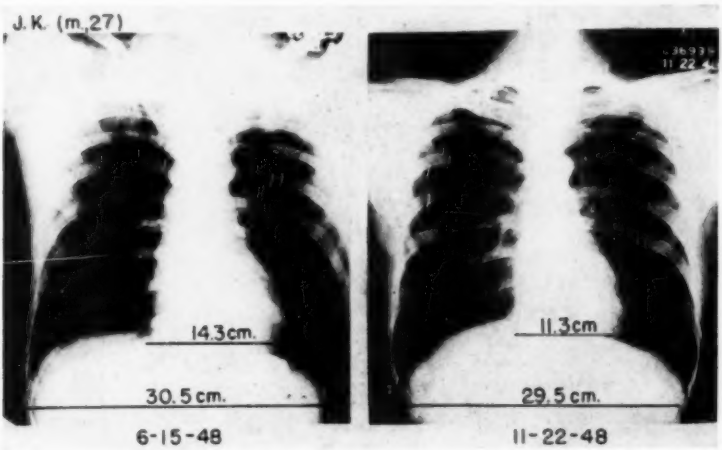

FIG. 11.

The heart is considerably smaller and the aneurysm of the posterior lateral wall of the left ventricle is now clearly visible in the A–P view (figure 9).

The patient, whose eyeground photographs and chest films are shown in figures 10 and 11, is an example of the effect of the rice diet on retinopathy and cardiac enlargement in chronic glomerulonephritis.

The patient was a 27 year old man who two years before admission to Duke Hospital, while in the Navy, had scarlet fever and acute glomerulonephritis, followed by chronic glomerulonephritis. He had been hospitalized for 16 months and treated with rest and various diets. During the month prior to admission, the patient had an exacerbation of his headache, noted blurring of vision and had a generalized convulsion, for which magnesium sulfate was given. At the start of the rice diet the blood pressure was 180

mm. of mercury systolic and 120 diastolic, the heart was enlarged, the vision considerably impaired, with bilateral marked papilledema, many hemorrhages and extensive exudates. The total phenolsulphonephthalein excretion in two hours was 7 per cent. The non-protein nitrogen was 90, the urea N 66.4 mg. per 100 c.c. of blood. The calcium was 7.8, the phosphorus 6.6, the

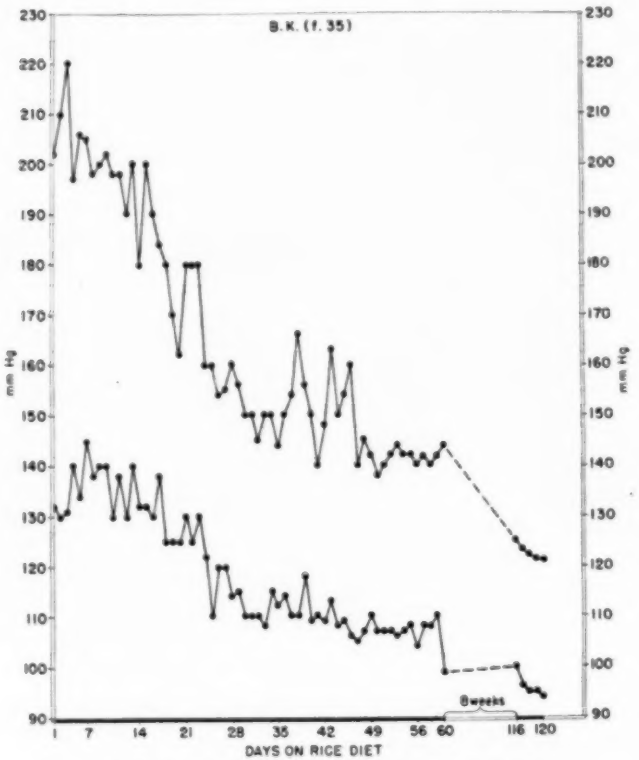

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FIG. 12.

cholesterol 350 mg. per 100 c.c. of serum. The serum chloride was 99.8 mEq. per liter.

After five months on the rice diet, the total PSP excretion in two hours was still only 10 per cent, but the NPN was 36, the urea N 15.8 mg. per 100 c.c. of blood. The calcium was 8.9, the phosphorus 5.1, the cholesterol 210 mg. per 100 c.c. of serum. The serum chloride was 88.2 mEq. per liter. The blood pressure was 137/99. The patient was asymptomatic; he had

regained his eyesight; papilledema, hemorrhages and most of the exudates had disappeared; the heart had decreased in size with a change in the transverse diameter of 27 per cent.

I have shown you some effects of the rice diet on edema, ascites, heart enlargement and retinopathy in patients with primary kidney disease. I will show you now some characteristic examples of the effect of the rice diet on hypertensive vascular disease without evidence of any primary renal disease. In more than 70 per cent of 777 patients most of whom were seriously ill and had failed to respond to other forms of treatment, the rice diet, given for periods of four to 1,150 days (average 92 days), has proved beneficial; that means that it has produced one or more of the following effects: decrease in the sum of systolic and diastolic blood pressure of at least

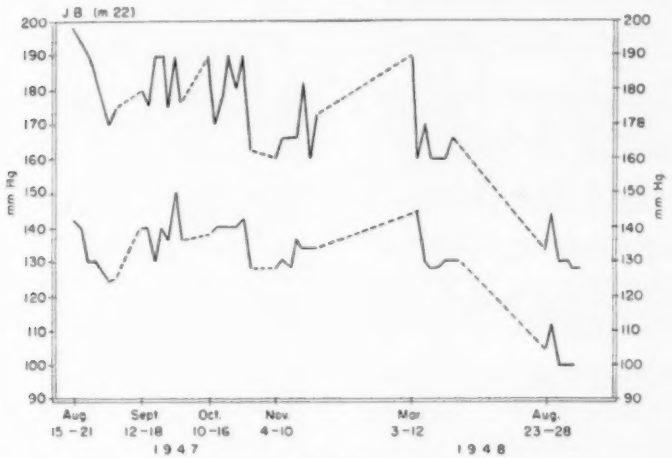

FIG. 13.

40 mm. Hg; reduction in heart size with change in the transverse diameter of 18 per cent or more; change in T_1 from completely inverted to upright; disappearance of severe retinopathy.

I will begin with three typical cases of so-called benign essential hypertension without serious cardiac, renal or retinal complications.

The first one is an example of a satisfactory response to the diet in about four months. It is the case of a 35 year old woman who had had hypertensive vascular disease for 11 years. There was no evidence of any renal excretory involvement. Of two brothers with hypertensive vascular disease, one had died of a stroke at the age of 37. For years, the patient did not feel up to par with increasing fatigue and exhaustion. There was a sensation of pressure and throbbing in the back of the head and in the eyes. From January to April, 1947, because of the appearance of retinal hemor-

rhages, rutin, vitamin K and sedatives were given; all activities had been severely restricted.

The patient began the rice diet in April, 1947. All medication was discontinued. On the first day of the diet, the blood pressure was 202/132; after three weeks of the diet the blood pressure was almost as high as before: 180/132. After 120 days, the blood pressure was 122/95 (figure 12). It has remained at this level until the present time (two years) in spite of the

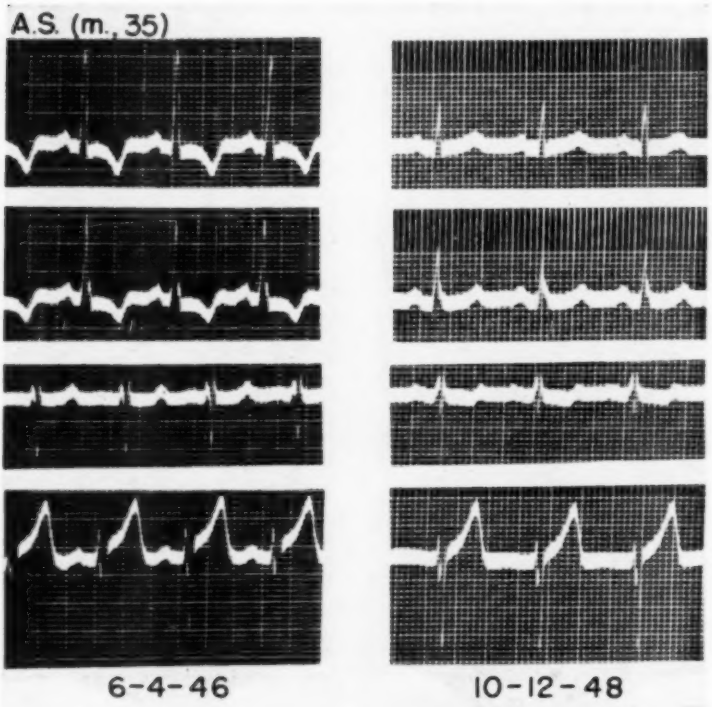

FIG. 14.

fact that two ounces of meat, one potato, 9 oz. of vegetables, one cup of coffee per day and 2 oz. of vegetable oil, 4 oz. of spaghetti per week, have been added to the diet. The patient has resumed her activities and is completely well.

The second case is an example of a rather slow response of hypertension to the diet. It is the case of a 22 year old man with benign essential hypertension without any history of kidney disease or evidence of renal excretory dysfunction. The patient had known about his hypertension for six months.

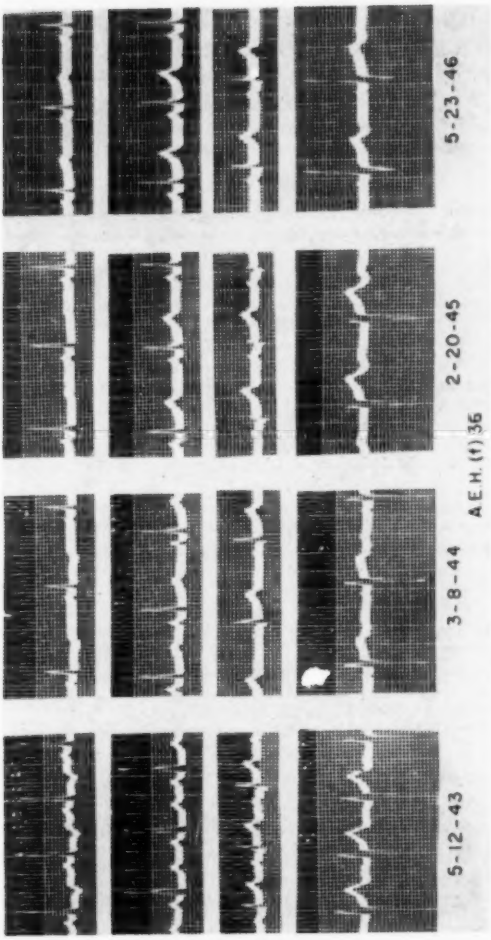

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FIG. 15.

He was asymptomatic except for intense headaches. He was started on the rice diet in New York. Since the blood pressure did not change in seven and one-half weeks, he came to Durham. During August, September and October, 1947, while he was staying in Durham continuously, the blood pressure remained persistently at a level of 170 to 190 systolic and 130 to 145 diastolic; the headache, however, disappeared. When the patient returned for reëxamination in November, 1947, and March, 1948, the blood pressure was as high as before. From June, 1948, on, i.e., *12* months after the rice diet was started, his physician in Alberta noticed that the blood pressure was decreasing. When the patient returned to us in August, 1948, after 14

TABLE VII

Blood Pressure Response According to Length of Time of Treatment

	Number of Patients	Percentage	Average Period on Rice Diet (Days)
4–1150 Days			
Total	777		92
Blood pressure not improved	226*	29%	72
Blood pressure improved	551	71%	101
4–74 Days			
Total	392		37
Blood pressure not improved	151**	38.5%	32
Blood pressure improved	241	61.5%	40
75–1150 Days			
Total	385		149
Blood pressure not improved	75***	19.5%	153
Blood pressure improved	310	80.5%	148

* Including 33 patients who died after 48 days (average).
** Including 25 patients who died after 32 days (average).
*** Including 8 patients who died after 100 days (average).

months on the rice diet, the blood pressure was as low as 128/100 (figure 13).

The shortest time in which we have seen a marked blood pressure decrease on the rice diet was four days. The average time is about three to four months.

Table 7 shows the positive and negative results of treatment in 777 patients with hypertensive vascular disease who followed the rice diet for four to 1150 days (average 92 days). There was a definite decrease of the blood pressure level in 71 per cent of the total group. The average of this decrease was from 198/116 to 150/96 in 101 days. If one differentiates the results according to the length of time the patients have been following the

diet, the importance of the time factor becomes obvious: In 392 patients who followed the diet for four to 74 days (average 37 days), there was a definite lowering of the blood pressure in 62 per cent. In 385 patients who followed the diet for 75 to 1,150 days (average 149 days), there was a definite lowering of the blood pressure level in 81 per cent.

The third case with benign essential hypertension is an example of a satisfactory response to the diet in one month. It is the case of a man now 47 years old who was well until he was 37. In March, 1940, he was seen in the New York Hospital. The blood pressure was 165 to 200 systolic and 105 to 135 diastolic. A diagnosis of hypertensive vascular disease was

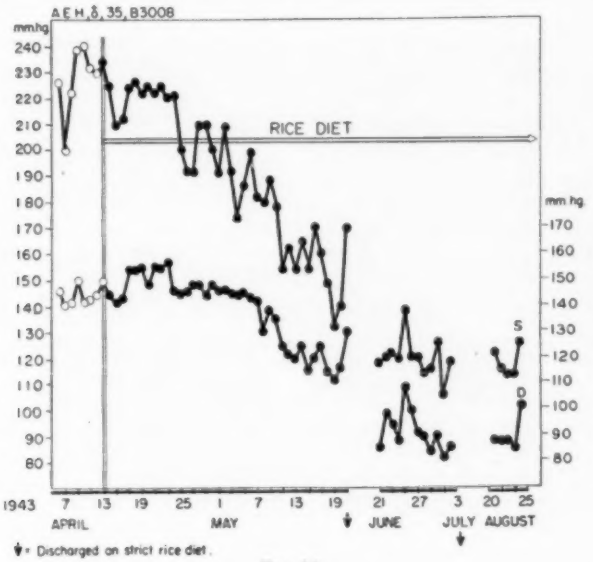

FIG. 16.

made. In January, 1941, he was seen in the Presbyterian Hospital. The blood pressure was found to be 200/140. One month later, the patient was seen in the Rockefeller Hospital with a blood pressure of 200/140. He was treated there by Dr. Henry Schroeder with tyrosinase until this had to be discontinued because of a severe shock-like reaction. As a matter of fact, this was the last patient whom Dr. Schroeder treated with tyrosinase. I like to show his record because Dr. Schroeder in the *American Journal of Medicine* in April of last year made the statement that the control periods preceding the rice diet might be too short to get an accurate base line for studying the effect of the diet. As is true for the majority of my patients, the base line for this patient was recorded by good observers not only over

a period of weeks or months but over a period of years. In this particular case, there are not only the figures of the New York and Presbyterian Hospitals but also those of Dr. Schroeder himself. After the tyrosinase treatment had failed, the patient went to Dr. Smithwick in Boston, where a lumbodorsal sympathectomy was done.

The sympathectomy did not help this patient. The blood pressure figures 14 months after the operation were even slightly higher than before. In 1945, the patient had a therapeutic trial with testosterone with no result. In March, 1945, when he came to us, he had tightness around the heart, headaches and swimming in the head. He had difficulty in walking and complained about a tendency to go toward the left and had at times run into

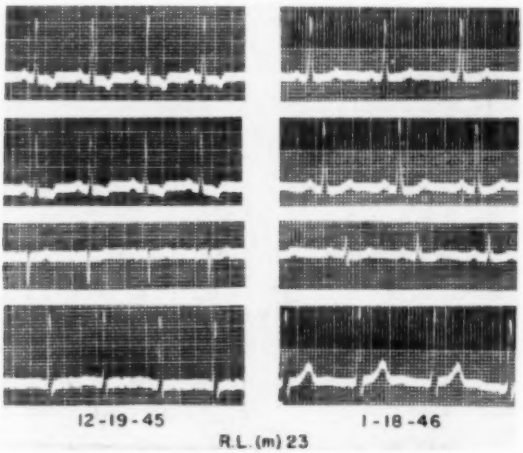

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FIG. 17.

walls. The blood pressure was 220/132. The average of daily blood pressure readings during 20 days while he was in the hospital on a 1,500 calorie diet was 197/129. No evidence of renal excretory dysfunction was found. PSP and urea clearance tests were normal. The rice diet was started on April 20, 1945. The blood pressure after one month of diet was normal and has remained normal to the present time. On February 24, 1949, it was 114/82. The diphasic T_1 in the electrocardiogram reverted to normally upright in seven months, and has remained upright since. The heart became smaller in size with a change in the transverse diameter of 12 per cent. The patient who was a sick man when he came to us in 1945, is now—four years later—well and active.

Patients such as these three, with so-called benign essential hypertension

are frequently told not to be concerned about their disease, unless some complication develops.

I believe the most appropriate time for treatment is before the more incapacitating complications of the disease have developed (cardiac breakdown, cerebral accidents, loss of vision and renal insufficiency). However, I will show you some typical electrocardiograms, chest films and eyeground photographs, which will illustrate that hypertensive vascular disease can be compensated to a great extent even when critical complications are already present.

Figure 14 shows the reversion of an abnormal electrocardiographic pattern to normal in a 35 year old man with hypertensive vascular disease of

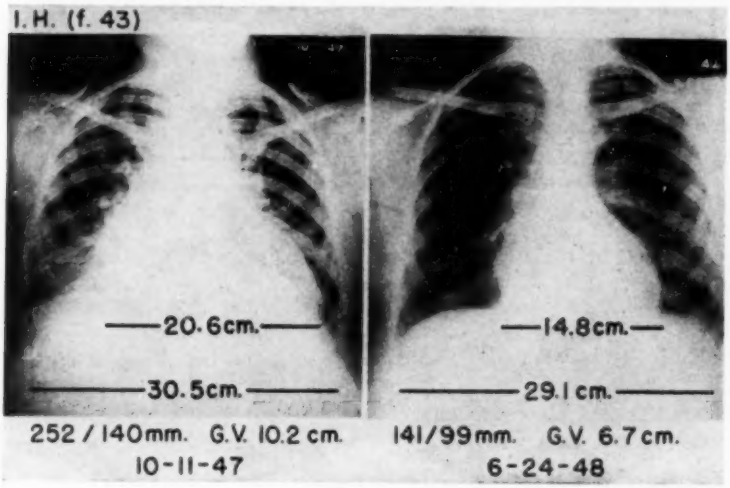

FIG. 18.

less than three years' duration. The change in the electrocardiogram is seen after 26 months on the rice diet. The blood pressure during this time decreased from an average of 205/122 to 150/103. Retinal hemorrhages and exudates disappeared. The deeply inverted T_1 became upright; the electrical axis improved.

Figure 15 illustrates the time factor in the gradual improvement of T_1. The patient was a 35 or 36 year old woman. Hypertension was known to be present for about one year. In May, 1943, T_1 was deeply inverted; in March, 1944, T_1 was low inverted; in February, 1945, low upright; in May, 1946, normally upright. This case also shows that there is neither a simple relationship between blood pressure drop and T_1 improvement nor between reduction in heart size and T_1 improvement. The blood pressure decreased

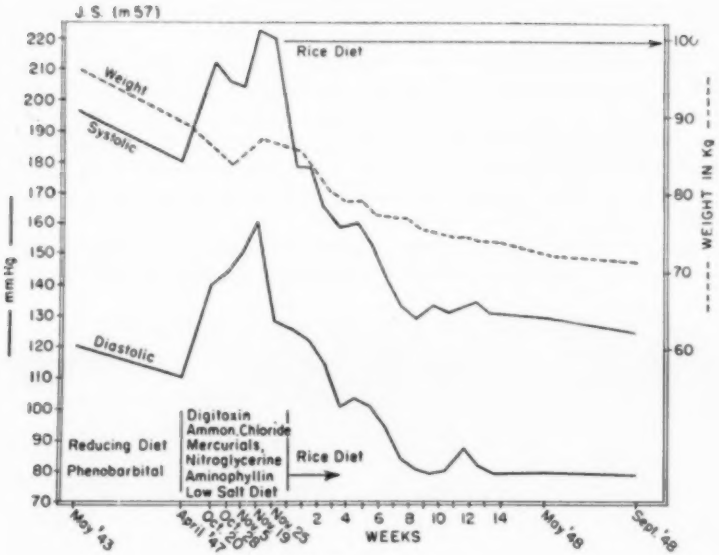

FIG. 19.

TABLE VIII

Changes of T_1 in 520 Patients with Hypertensive Vascular Disease after Rice Diet

Number of Patients	T_1 Before Rice Diet	T_1 After Rice Diet	Period on Rice Diet (Average)
	No Change (388)		
68	Inverted	Inverted	7 months
34	Diphasic	Diphasic	8 months
286	Upright	Upright	11 months
	Change in direction to inverted (10)		
0	Upright	Inverted	
5	Diphasic	Inverted	8 months
5	Upright	Diphasic	4 months
	Change in direction to upright (122)		
38	Diphasic	Upright	9 months
32	Inverted	Diphasic	13 months
52	Inverted	Upright	10 months

from 220/150 to 124/85 (figure 16) and the heart became normal in size within 10 weeks on the rice diet. Three years were required for the inverted T_1 to become normally upright.

Figure 17 shows the reversal of an inverted T_1 in the shortest period of time we have seen, one month. It is the electrocardiogram of a 23 year old man with hypertensive vascular disease, uncomplicated for three years, in the malignant phase with severe neuroretinopathy for three months. During the first month of the rice diet in which T_1 became normal, the blood pressure

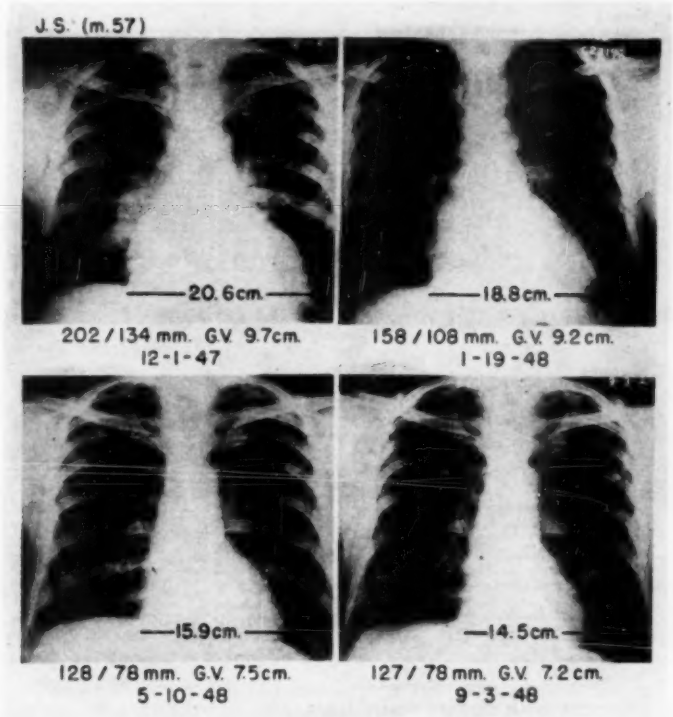

FIG. 20.

level decreased from an average of 222/148 to an average of 153/112. A normal blood pressure was reached only after two more months on the diet.

The T waves in Lead I were evaluated in 520 patients. None of these patients received digitalis or any other drug. All electrocardiograms were made with the patient at rest and in recumbent position. In 286 electrocardiograms which were normal at the start and in 102 electrocardiograms

which were abnormal at the start, no change occurred. In 132 electrocardiograms, a change did occur. In 10 in the direction from normal toward inverted. In 122 in the direction from abnormal to upright (table 8).

Figure 18 shows two chest films as an example of the reduction in heart size produced by the rice diet. It is the case of a 43 year old woman who had had hypertensive vascular disease for 14 years. It remained uncomplicated for 11 years. Then auricular fibrillation and heart failure developed with liver enlargement, edema, dyspnea and substernal pain. The

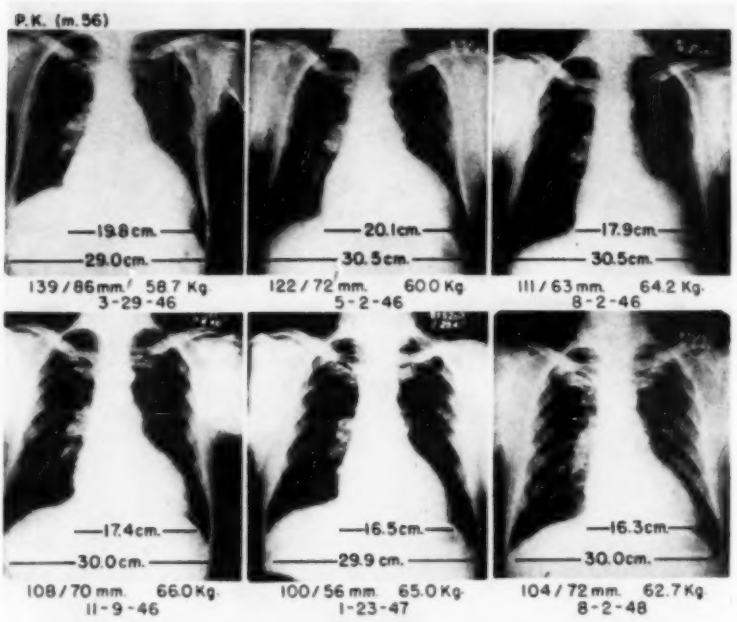

FIG. 21.

usual treatment with dietary restrictions, rest and digitalis was given with no improvement. Within eight months on the rice diet, the blood pressure decreased from 252/140 to 141/99, and the heart became smaller in size with a change in the transverse diameter of almost 40 per cent. The patient became asymptomatic and is now doing rather strenuous work.

The next case is an example of the length of time required for a heart which is enlarged and disfigured by the disease to change its size and shape back towards normal. The patient was a 57 year old man who had known he had hypertensive vascular disease for four years. Hypertensive heart

disease had become apparent in April, 1947. It was treated with digitoxin, ammonium chloride, mercurials, nitroglycerin, aminophyllin, weight reduction, salt-restricted diet. In spite of this medication and a weight loss of 30 pounds, the blood pressure increased and the heart failure became worse. When the patient came to us, the rice diet was started, and all medication including digitalis was immediately discontinued. The edema disappeared in 20 days; the blood pressure returned to normal in two months (figure 19). A decrease in heart size was noted after six weeks with a change in the transverse diameter of 8.7 per cent; after five months there was a change of 29 per cent; after nine months there was a change of 42 per cent (figure 20).

FIG. 22.

The patient became completely asymptomatic and has been without any medication for the past 14 months.

Chest films of 286 patients taken before and after one month or more of dietary treatment were measured for comparison (no digitalis or other drugs were given after the day the first chest film was taken). In 15 of the 286 patients (i.e. in 5 per cent), the heart became larger with an average increase of 2.6 per cent. In 146 patients there was a decrease in heart size with a change in the transverse diameter of 6.2 per cent (average), in 106 patients there was a decrease with an average change of 14.2 per cent and in 19 patients a decrease with an average change of 24.4 per cent (table 9).

I do not think that the improvement in the electrocardiographic pattern or the decrease in heart size or the disappearance of papilledema, hemor-

TABLE IX

Effect of Rice Diet on Heart Size: Average Changes in Transverse Diameter of Heart in 286 Patients with Hypertensive Vascular Disease

	Change		Average Period of Rice Diet (days)
	Diameter of Chest %	Transverse Diameter of Heart %	
15 patients with *increase* of 0–8.0%	+0.8	+ 2.6	184
146 patients with *decrease* of 0–9.9%	−0.7	− 6.2	112
106 patients with *decrease* of 10–19.9%	−0.3	−14.2	114
19 patients with *decrease* of 20% or more	−2.2	−24.4	187

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rhages, and exudates in the eyegrounds occurs as a simple consequence of a decrease in blood pressure. I have seen quite a few patients in whom these improvements have occurred in spite of the fact that the blood pressure remained at exactly the same level as before. They, likewise, occur in the many instances where vascular retinopathy and/or heart enlargement are present without hypertension.

Figure 21 is an example of the compensation of heart failure and the reduction of heart size in a patient who had gone through a fairly complete list of therapeutics. When he came to us in March, 1946, he was 56 years old. He had had nephrolithiasis and had developed hypertension and hypertensive heart disease. Nephrectomy on the left side was done in 1940 in

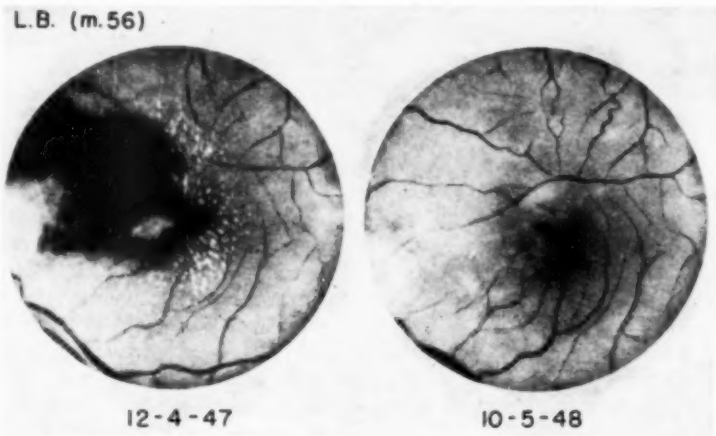

FIG. 23.

the hope of arresting his vascular disease. In spite of this, the disease continued and a left bundle branch block developed. When heart failure gradually increased, digitalis, squill, mercupurin, ammonium chloride, sedatives and salt-poor diet were tried.

The first chest film of March 1946, showed a greatly enlarged heart. There was edema, liver enlargement, and ascites. All medication was immediately discontinued and the rice diet started. Five weeks later the transverse diameter of the heart was 3 mm. larger, but the patient had lost most of his edema and was no longer dyspneic. The patient ate one pound of rice (dry weight) and one pound of dextrose daily and gained over 7 kg. during

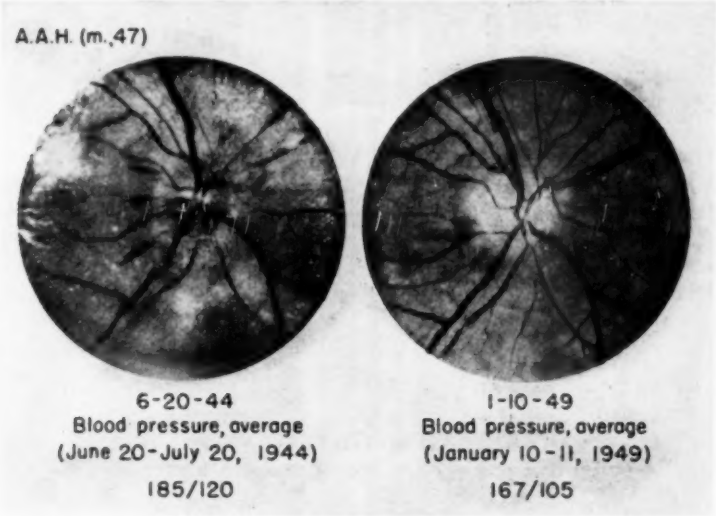

FIG. 24.

seven months in spite of the loss of edema. Four months after the start of the diet the transverse diameter of the heart had decreased from 19.8 to 17.9 cm.; after seven months from 19.8 to 17.4 cm.; after 10 months from 19.8 to 16.5 cm. No medication has been given for the past three years. The patient is feeling well and is completely asymptomatic. The transverse diameter of the heart is now 16.3 cm., which means an overall change of more than 20 per cent. I showed the patient these heart pictures, boasting about the result. In return, the patient sent me a Christmas card with pictures of his face "before and after the rice diet" (figure 22). They are perhaps not uninteresting even from our mechanistic point of view. The first photograph shows the characteristic face of a patient with advanced heart disease,

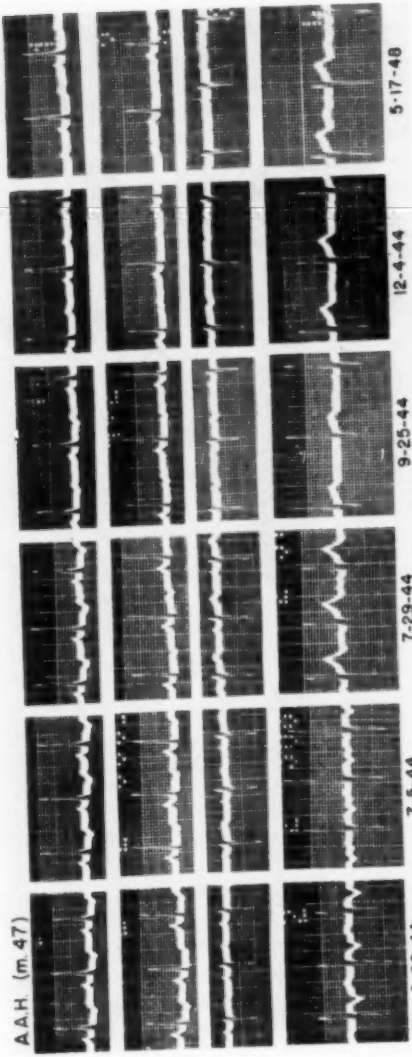

FIG. 25.

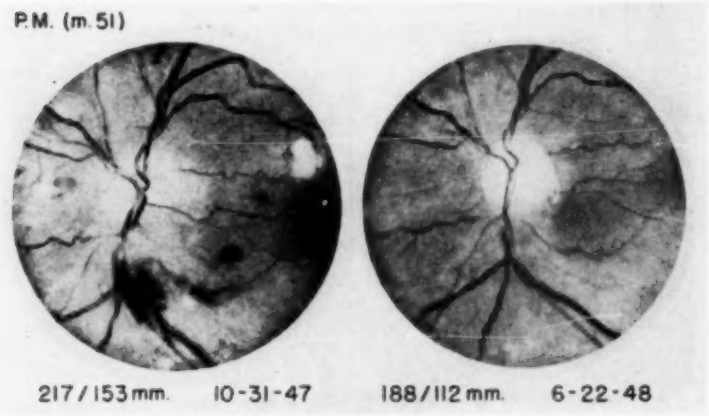

FIG. 26.

drawn, emaciated, prematurely aged, like that of a victim of starvation. The second photograph shows a well nourished, healthy man: one might say that the face has gained what the heart has lost.

Vascular retinopathy responds to the rice diet just as well as myocardial disease. The improvement of the retinopathy occurs no matter whether the blood pressure decreases or not.

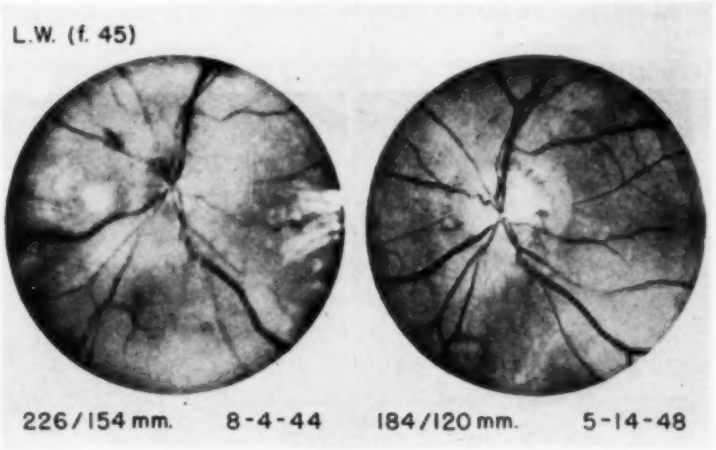

FIG. 27.

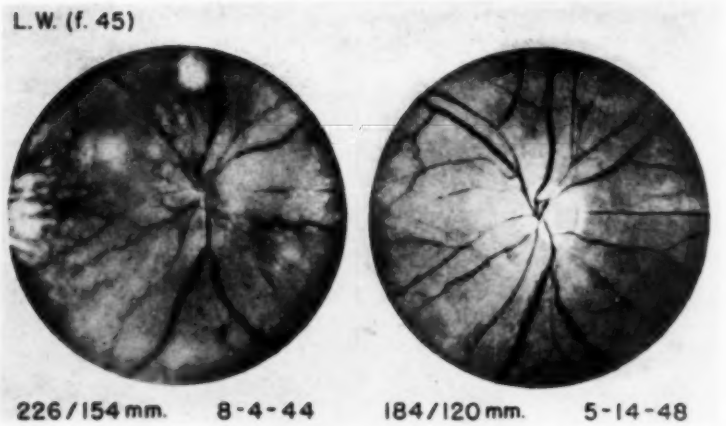

FIG. 28.

The eyeground pictures of three cases are shown as examples of the disappearance of papilledema, exudates, and hemorrhages, in spite of persistent hypertension. The first patient is a 56 year old man with hypertensive vascular disease which had been uncomplicated for 10 to 15 years. One month before he came to us he became blind in his left eye. The pictures (figure 23) show the disappearance of massive hemorrhages and exudates in 10 months on the rice diet. The patient regained his eyesight and is now well and active. The blood pressure has decreased but is still not normal.

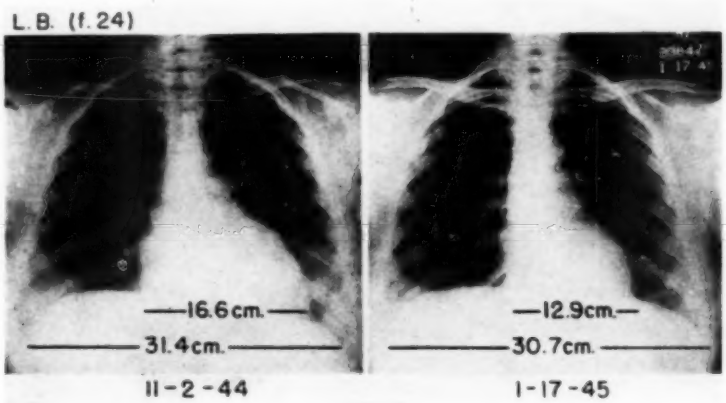

FIG. 29.

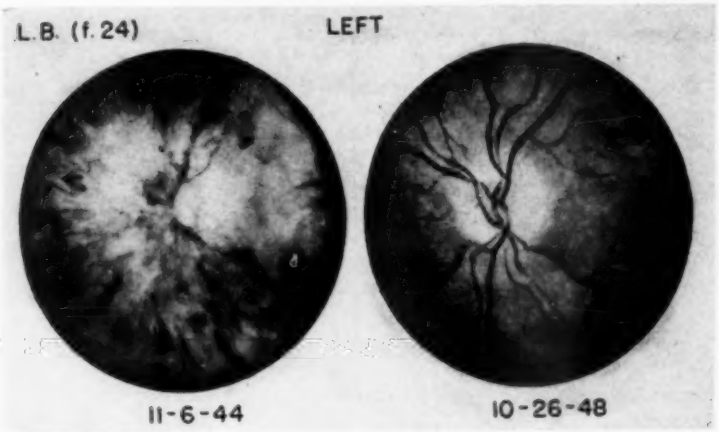

FIG. 30.

The second case is that of a man who was 47 years old when he came to us almost five years ago. He had been suffering from periodic attacks of severe headaches for years, but had known of his hypertension only for three months. He had not been conscious of any impairment of vision until I asked him to close his left eye and he found he was unable to read the headlines of a newspaper with his right eye. In one and one-half years of treatment with the rice diet, the exudates in the macula disappeared. The papilledema and hemorrhages cleared up completely and the eyesight was restored

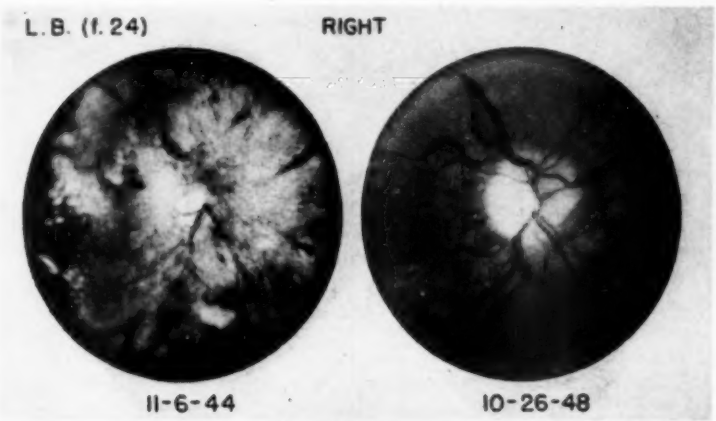

FIG. 31.

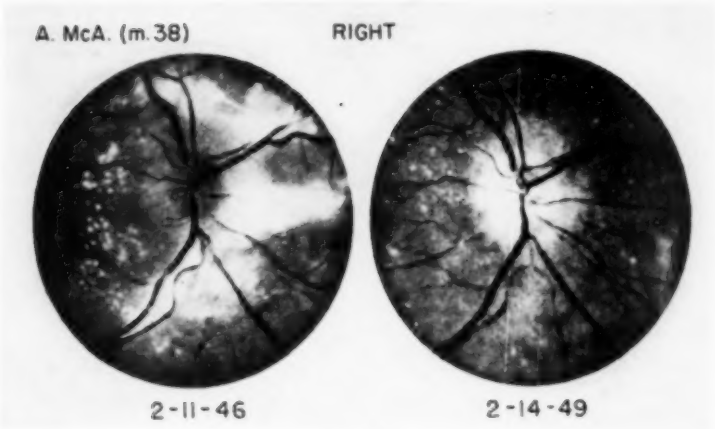

FIG. 32.

(figure 24). The heart, which was involved, also improved; the inverted T_1 in his electrocardiogram became normally upright (figure 25). The blood pressure has decreased but is not normal.

The third patient is a 51 year old man with hypertension known for 10 years. He had had progressive heart failure for seven months. There was hypertensive neuroretinopathy with papilledema, hemorrhages, and exudates, which cleared up in eight months on the rice diet (figure 26). The blood pressure did not become normal, but dropped from 217/153 to 188/112.

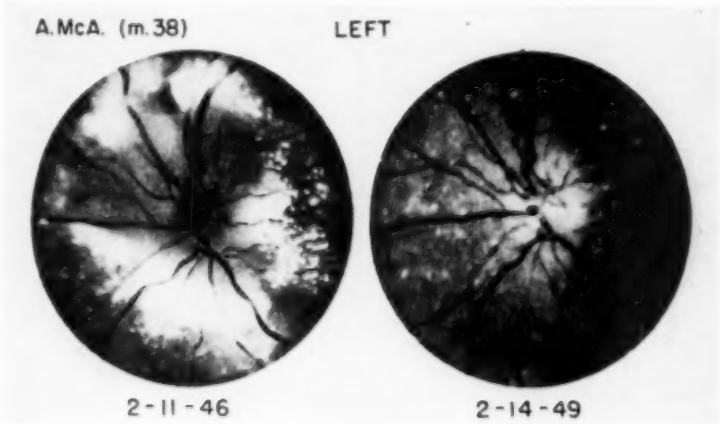

FIG. 33.

I have shown you pictures of patients who had essential hypertension with severe complications. We classify this type of hypertension as benign because of its slow course, although the term benign may lose its sense when the patient becomes blind from retinal disease or when he dies of heart failure, myocardial infarction, cerebral vascular accident or uremia. Moreover, the possibility always exists that any benign vascular disease may suddenly change into the malignant form. The last three patients whose eyeground photographs I showed you presented some of the signs said to be characteristic of malignant hypertension, the high diastolic blood pressure and

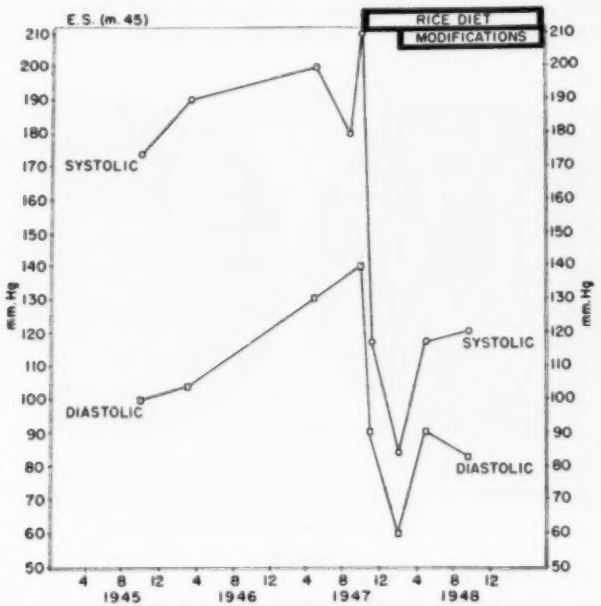

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FIG. 34.

papilledema, hemorrhages and exudates. However, the eyegrounds did not show the picture of the explosive retinopathy which we associate with true malignant hypertension.

The following photographs are shown as examples of the effect of the rice diet on patients with full blown malignant hypertension.

The first case is that of a 45 year old woman who came to us in 1944 with a history of hypertension of four months' duration, apparently malignant from the onset. The eyegrounds show the typical picture of malignant neuroretinopathy. The patient followed the strict rice diet for one

year, then a modified rice diet. The blood pressure decreased from a level of 226/154 to a level of 184/120. The retinopathy healed completely (figures 27 and 28). Not only did the patient not die but after more than four and one-half years she is up and around and has no complaints.

The second patient is a 24 year old woman who had had an uncomplicated hypertension for five years. This benign hypertension had become malignant one month before she came to us (October, 1944). In 24 days on the rice diet, the blood pressure decreased from 233/157 to 118/80. The heart became smaller in size with a change in the transverse diameter of 22 per cent in 11 weeks (figure 29). Papilledema, hemorrhages and exudates disappeared in about three months. As the eyeground pictures of October, 1948, show, the retinopathy did not recur (figures 30 and 31). The

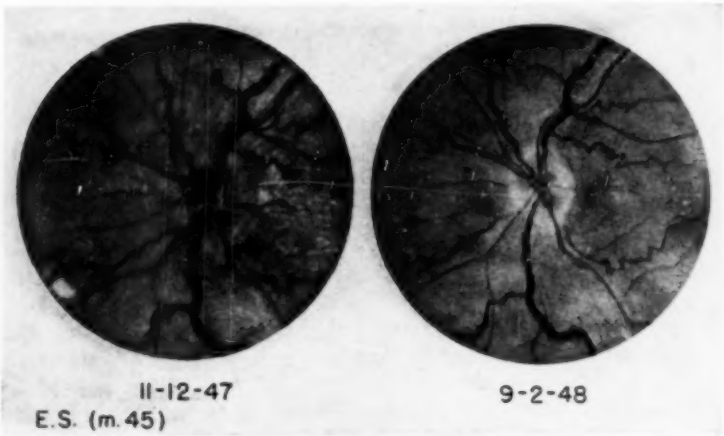

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FIG. 35.

patient not only did not die of her malignant hypertension, but after more than four years is now well and doing strenuous work on her farm.

The third patient is a 38 year old man who had had hypertensive vascular disease for one year. The hypertension had been obviously malignant for about three months before he came to us. This case has been chosen as an example of a rather slow response to the rice diet. Definite improvement of the extensive neuroretinopathy was not seen until after one year. The inverted T_1 in the electrocardiogram did not become upright until after two and one-half years, and it took almost three years for the blood pressure to come down to a significantly lower level (figures 32 and 33).

As a kind of summary, let me end with a case which shows not only the success but also the possible dangers of the rice diet. The patient, a busi-

ness man from New York, had had periodic check-ups since 1932 when he was 30 years old. The blood pressure had always been normal until 1941 when a slight elevation was noted. It climbed slowly during the following years. In 1945, it was 170/100, in 1946 190/100, in the Spring of 1947 190/130. In spite of this, the patient was completely asymptomatic. Both family physician and consultant specialist advised treatment with weight reduction, rest, sedatives and restriction of smoking. In September, 1947, the patient suddenly developed a severe headache with visual disturbances and consulted an ophthalmologist who found retinal hemorrhages, exudates, and papilledema and made a diagnosis of retinopathy of malignant hypertension. Another medical specialist was consulted who found a blood pressure of 202/144, confirmed the diagnosis of malignant hypertension and sent

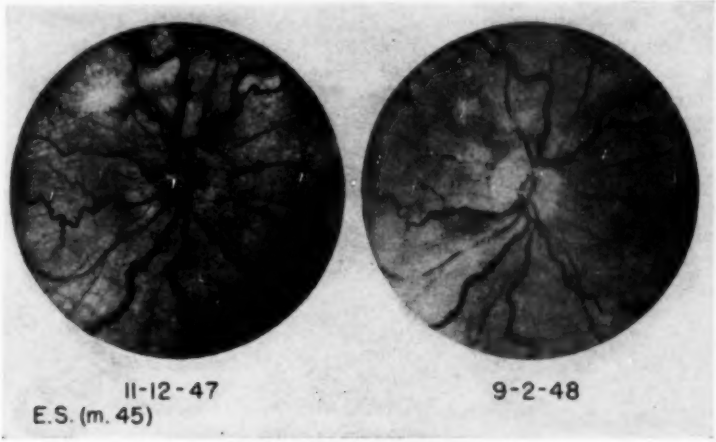

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FIG. 36.

the patient to a surgeon in the New York Hospital for sympathectomy. The surgeon made the same diagnosis and recorded the same findings. After eight days of observation, a sympathectomy was scheduled for Monday, October 27, 1947. The evening before the operation, the patient decided to try the rice diet first and came to Durham. He presented the typical picture of malignant hypertension. The blood pressure was 210/140, in spite of sedatives; the eyegrounds showed extensive neuroretinopathy. On the rice diet, the blood pressure decreased rapidly. As a matter of fact, it decreased so much that after three months the patient had a blood pressure of 85/58 while lying and 60/30 while standing. A marked hypochloremia with elevation of urea nitrogen and non-protein nitrogen was found and the diet had to be modified greatly by the addition of toast, meat and all kinds of vege-

tables. The blood chemistry returned to normal and the blood pressure was regulated at a level of 110/77 within two weeks (figure 34). All the signs and symptoms of the malignant hypertension have disappeared; papilledema, retinal hemorrhages and exudates have cleared up completely; the engorged and tortuous veins are smaller in caliber and straighter (figures 35 and 36). However, not only the malignant but also the benign hypertension has disappeared. The blood pressure, which had been above normal for six years, is now (one and one-half years after the start of the rice diet) 116/76, although the patient has resumed playing his 18 holes of golf and eats a fairly liberal diet.

Ten years ago, I used to teach, what was generally taught and is still written in textbooks published as late as 1947, that the presence of advanced neuroretinopathy in malignant hypertension is an ominous prognostic sign indicative of the terminal stage of an irreparable disease. My experience with the rice diet has taught me that not only can so-called benign hypertensive vascular disease be effectively treated even when critical complications are present but also that malignant hypertension, in spite of advanced neuroretinopathy, may either be changed into the benign form of hypertension or made to disappear completely. The important result is not that the change in the course of the disease has been achieved by the rice diet but that the course of the disease can be changed.

VIRAL HEPATITIS: PROBLEMS AND PROGRESS *

By JOHN R. NEEFE, M.D., *Philadelphia, Pennsylvania*

THE problems associated with certain viral diseases of the liver have been the subject of intensive study during recent years. As methods permitting specific etiologic diagnosis are not available, the non-specific term "viral hepatitis" has been found useful for reference to the syndrome under consideration. "Viral hepatitis" thus includes those forms of hepatitis caused by hepatotropic, filterable, infectious agents which have not yet been identified with specific serological responses but which produce, as their outstanding manifestation, evidences of liver injury, which may or may not be associated with phenomena suggesting an infectious origin.

The available evidence indicates that at least two "virus-like" agents are concerned.[1, 2] One, hereafter referred to as virus IH, has been identified primarily with the clinical and epidemiological syndrome of infectious (epidemic) hepatitis. The other, hereafter referred to as virus SH, has been associated with the "homologous serum hepatitis" syndrome which characteristically develops two to five *months* after the occurrence of an opportunity for parenteral entry of the virus. The term "homologous serum hepatitis" really is an epidemiological term indicating the source of the infectious agent, but it unfortunately has acquired a misleading etiological implication in that the term has come to be synonymous with the hepatitis syndrome occurring after the long two to five month interval. However, virus IH also may be transmitted by blood or its products and be responsible for hepatitis after a two to six week interval. This syndrome also must be regarded as "homologous serum hepatitis," and it is therefore important to recognize that hepatitis syndromes occurring from two weeks to six months after exposure may be of viral origin and represent "homologous serum hepatitis."

The literature in recent years has been concerned almost entirely with the *advances* in knowledge concerning "viral hepatitis." It has seemed worthwhile, therefore, to refer briefly to some of the more important advances and then to devote the majority of the present discussion to a consideration of some of the remaining problems and current investigations directed toward their solution.

RECENT ADVANCES

As the recent advances in knowledge concerning viral hepatitis have been reviewed in detail elsewhere,[1, 2] only those pertinent to the present discussion

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will be enumerated here. References to the original work and those responsible for it can be found in the review articles cited.

1. *Etiology:* (*a*) Differentiation of the two "virus-like" agents by means of studies in human volunteers; (*b*) Accumulation of information concerning certain of the physical properties of these agents including information indicating their resistance to many procedures which destroy or inactivate most bacteria and other viruses.

2. *Epidemiology:* (*a*) Demonstration of feces and blood as the principal human sources of the etiological agents; (*b*) Accumulation of evidence supporting the intestinal-oral route as a common mechanism of spread of the "IH type" virus; (*c*) Recognition of the rôle of blood and blood products as a source of both virus IH and virus SH and of various mechanisms of transfer of these viruses in blood to humans; (*d*) Demonstration that hepatitis virus may be water-borne and that certain methods of water disinfection may not be adequate under some circumstances; (*e*) Accumulation of data on incidence indicating the public health and military importance of the disease.

3. *Clinical Aspects:* (*a*) Establishment of the existence of a non-icteric form of the disease; (*b*) Elaboration of the clinical manifestations and their significance; (*c*) Recognition of the importance of hepatic tests and liver biopsy in diagnosis, management and prognosis; (*d*) Recognition that the disease may be associated with a significant mortality and morbidity and may be a cause of chronic liver disease; (*e*) Recognition of the possible association of certain etiologically obscure forms of chronic liver disease with previous apparent or inapparent infection with hepatitis virus.

4. *Prevention and Control:* (*a*) The discovery that human immune serum (gamma) globulin is highly effective in the prevention of virus IH hepatitis when administered to exposed persons during the incubation period prior to the onset of symptoms; (*b*) The recognition of certain mechanisms of transmission of hepatitis virus in blood, permitting the eradication of certain of those mechanisms; (*c*) Recognition of the potential danger of "water-borne" hepatitis virus and the unreliability of certain technics for disinfection of water; (*d*) Demonstration of the effectiveness of heat in the inactivation of hepatitis virus in human serum albumin solutions; (*e*) Development of a practical technic for large scale ultraviolet irradiation of plasma which has been effective in the inactivation of at least one strain of hepatitis virus in plasma.

Consideration of Certain Remaining Problems

Etiology: To the present time, no extra-human host for hepatitis virus has been recognized. The human host, therefore, remains as only known source of hepatitis virus. Hepatitis virus IH would appear to account satisfactorily for most of the naturally occurring epidemics of hepatitis, certain cases of so-called "homologous serum hepatitis," and some sporadic cases. However, a large number of the sporadic cases occurring at the

present time are characterized by certain clinical features which are more consistent with the clinical syndrome that was observed in association with hepatitis virus SH under experimental conditions. As these differences in the clinical syndromes of virus IH and SH hepatitis, as observed experimentally, have been described in detail elsewhere,[1, 3] the summary in table 1

TABLE I

Clinical Differences between Virus IH and Virus SH Hepatitis as Observed in Volunteers

Observation	Hepatitis	
	Virus IH	Virus SH
1. Type of onset	Abrupt	Insidious
2. Constitutional symptoms with onset	Marked	Minimal
3. Fever with onset	Present	Absent
4. Laboratory evidence of hepatic injury in association with clinical onset	Delayed 2 to 7 days	Often present before clinical symptoms

will suffice for the present discussion. Although it must be *strongly* emphasized that these differences are *not* sufficiently reliable or consistent to permit their use for clinical differentiation between virus IH and SH hepatitis, the similarity between the clinical features of many sporadic hepatitis cases and those of the virus SH syndrome leads one to suspect that some of them may be due to this virus. Thus, in a spot survey of approximately 250 cases of "viral hepatitis" hospitalized during June 1947 in the United States Army Hepatitis Center at Bayreuth, Germany (120th Station Hospital), Dr. W. Paul Havens, Jr. and I were impressed with the fact that approximately 85 per cent of the patients had had a relatively silent, insidious, almost asymptomatic, afebrile onset of jaundice. This contrasted strikingly with the usual type of onset of the naturally occurring disease observed in this and other overseas theatres during the recent war, namely a sharp, febrile onset associated with marked constitutional symptoms. In addition, it was found that almost all of the cases hospitalized in the Center at that time were sporadic, only a small proportion of the total cases having arisen in association with small, localized outbreaks. Perhaps of some significance was the fact that almost every patient in this group had had some exposure to the "syringe-needle" source of hepatitis virus during the six month period prior to the onset of the disease.

It seems reasonable, therefore, to suspect that at least some of the cases of sporadic viral hepatitis may be due to virus SH.

The possibility of an etiologic relationship between viral hepatitis and certain etiologically obscure forms of chronic liver disease, such as those illustrated by the following brief case abstracts, also is of considerable interest and importance.

Case N92–49. A 19 year old white female had a silent, asymptomatic, afebrile onset of jaundice with minor gastrointestinal symptoms during the spring of 1948.

Jaundice has persisted to the present time (one year) with only minor constitutional symptoms. Hepatic tests indicate moderately severe, active hepatic disturbance of the type associated with acute viral hepatitis. Needle liver biopsy reveals a dense infiltration of the portal triads with lymphocytes and plasma cells. Some of the lobules also show infiltration with these cells. A moderate increase in connective tissue is apparent in some of these triads with strands penetrating some of the lobules. The hepatic cells show varying stages of degeneration and regeneration.

Case N96–49. In 1945, an 18 year old male student reported that friends had noted scleral icterus. History and physical examination were negative except for scleral icterus and several recent transient episodes of upper abdominal discomfort, anorexia, and brief nausea. Hepatic tests revealed a retention type of jaundice. Tests for hemolysis were negative and the phenomena were thought to be most consistent with a diagnosis of so-called "physiological hyperbilirubinemia." From 1946 to the present time, he experienced one to two day periods of mild constitutional and gastrointestinal symptoms associated with hyperbilirubinemia (retention type); during the last year he occasionally has had a transient elevation of urine urobilinogen and intermittently positive "flocculation tests." These symptomatic episodes occurred once or twice each month. His interval health otherwise has been excellent. Liver biopsy revealed a normal architectural pattern. An apparent slight increase in the amount of fibrous tissue in a number of the portal triads was noted and several contained a definite infiltration with lymphocytes, histiocytes and plasma cells. In several areas, the connective tissue had the appearance of hyaline degeneration. A number of the hepatic cells had double nuclei and the appearance in certain areas suggested active regeneration of hepatic cells.

Case N69–48. This 47 year old white female developed pruritus, malaise, and minor gastrointestinal symptoms in the spring of 1947. The symptoms persisted and mild jaundice was noted several months later by a physician. In spite of a six month period of bed rest and all the therapeutic measures commonly employed in the management of chronic liver disease, the jaundice persisted and the serum albumin gradually decreased. When seen in the fall of 1948, she presented mild jaundice, numerous spider nevi, massive hepatomegaly (involving particularly the left lobe to an extent that suggested the presence of a focal lesion), and an enlarged spleen which filled the entire left abdomen from the costal margin to the pelvic inlet. Evidences of hypersplenism including moderately severe anemia, thrombocytopenia, and pronounced leukopenia were present. Hepatic tests revealed evidence of severe hepatic injury and liver biopsy revealed diffuse severe hepatic fibrosis, cellular infiltration, and various stages of degeneration and regeneration of hepatic cells.

It seems possible that these and certain other hepatic syndromes may represent clinical variants of chronic hepatitis initiated by the recognized, or other as yet unrecognized, strains of hepatitis virus. Determination of whether such chronic disease, if related to viral hepatitis, is the result of continued activity of the viral agent, or to some other process initiated by it, will be essential to the development of more effective methods of treatment.

Another clinical and etiological problem which may have some relationship to subclinical infection with hepatitis virus has become apparent during the course of studies on persons who have had varying degrees of recognized exposure to hepatitis virus. During the past two years, studies in our laboratory [4] in collaboration with Drs. Charles H. Kurtz, Hugo Dunlap Smith, John G. Reinhold and S. Clay Williams have revealed a surprisingly high incidence of laboratory findings suggesting mild hepatic disturbance in

groups of young adults who previously had had either maximal or minimal exposure to hepatitis virus without having developed clinically recognizable infections. The incidence of such findings in both groups has approximated 10 per cent. It is hoped that continued observation of these groups over a period of years will help to clarify the significance of the present subclinical abnormalities.

Epidemiology: Little additional information concerning the epidemiology of naturally occurring outbreaks of viral hepatitis has been obtained during the past two years. The probable importance of contaminated water as a source of some outbreaks deserves further emphasis. Epidemiological and experimental evidence of the natural transmission of hepatitis virus IH by this means was first reported in 1945 by the author and Dr. Joseph Stokes, Jr.[5] Subsequently, additional outbreaks have been traced to this source on the basis of epidemiological evidence and very recently Drs. John Farquhar and Joseph Stokes, Jr.[6] have studied a localized rural epidemic in which epidemiological data provided strong evidence that the virus was transmitted by water from a contaminated well.

In respect to the problem of *blood transmitted hepatitis virus,* evidence of the probable importance of the asymptomatic carrier is slowly accumulating. We have previously reported circumstantial evidence indicating that such a carrier was the source of a hepatitis virus that was present in a pool of mumps convalescent plasma in which his plasma had been included.[7] Experimental studies have shown conclusively that hepatitis virus was present, at least intermittently, in the blood of inoculated volunteers during the long asymptomatic interval between inoculation and the onset of clinically recognizable symptoms and signs of the disease.[8, 9]

Of particular interest in this respect is the recent recognition by Drs. J. Edward Berk and Leonard Malamut[10] of a professional donor who may represent a true asymptomatic long term carrier of hepatitis virus. Three of their patients who had developed the syndrome of homologous serum hepatitis had received blood from this professional donor at different times over an eleven month period during 1947–48. One of these patients had received no other blood or plasma. The onset in all three cases was approximately six weeks after transfusion. Subsequently, it was found that a patient who had received his blood in 1945 (no other blood or plasma) had developed jaundice within three months, the exact interval not being certain. Thus at least four cases of homologous serum hepatitis may be traceable to blood obtained from this professional donor at different times over a three year period. The donor had no history of recognized hepatitis or other liver disease. However, study of the donor by Berk and Malamut revealed the presence of hepatic dysfunction and a liver biopsy provided histologic evidence of chronic liver disease with diffuse fibrosis. The rôle of the hepatitis virus in the donor's hepatic disease is not clear as he also was a chronic alcoholic. It is hoped that transmission studies with this donor's serum, which are planned by Drs. Joseph Stokes, Jr. and John Farquhar in

collaboration with Drs. Berk and Malamut, will provide the needed confirmation of this important epidemiological observation. Of great interest and importance is the suggestive evidence of the existence of a carrier state over at least a three year period.

These observations provide further evidence of the probable frequency and importance of asymptomatic carriers in the epidemiology of this disease and the serious implications justify a reconsideration, at this time, of the general problems associated with blood transmitted hepatitis virus. Some of the factors contributing to the difficulties in solution of this problem are as follows [1, 2]:

1. Hepatitis virus may be present in high concentration in blood since minute quantities of plasma (.01 ml.) have induced the disease in volunteers.
2. Hepatitis virus may be present in blood without associated clinical symptoms or signs.
3. Whether viremia persists or recurs after recovery from acute hepatitis is not known.
4. No practical clinical method for demonstrating the presence of hepatitis virus in blood or its products has been developed.
5. Hepatitis viruses survive for long periods under widely varying conditions and resist many procedures which eliminate or inactivate many infectious agents.
6. Most procedures capable of inactivating or destroying hepatitis virus cannot be applied to blood or plasma without rendering them unsatisfactory for human use.
7. Active immunization against either virus IH or virus SH is not yet possible and human immune serum (gamma) globulin apparently does not afford passive protection against virus SH.
8. The disease has a high morbidity, may be responsible for the initiation of chronic hepatic disease, and has a significant mortality rate, particularly when superimposed on other conditions.

In view of these problems, a knowledge of the risk of transmission of hepatitis virus involved in the therapeutic use of blood and plasma becomes a matter of importance to all physicians. The lack of a specific diagnostic test, the difficulties of adequate follow-up have made the reliability of available data on the incidence of hepatitis following blood and plasma transfusion somewhat uncertain. However, the available information suggests that the minimal incidence of hepatitis associated with blood and plasma may be approximately as follows [11, 12, 13]:

Material	Incidence of Hepatitis
Whole Blood	0.6 to 0.8%
Small plasma pools (5–10 units)	1.5%
Large plasma pools (1000–5000 units)	4.5 to 12%

On the basis of these figures which do not include the cases of hepatitis without jaundice, there appears to be strong evidence of a serious risk in the use of large plasma pools and a smaller, but significant, risk in the use of either small plasma or whole blood pools. The risk of whole blood and small plasma pools often is increased by the frequent need for multiple transfusions by the same patient.

Unfortunately, the problems associated with hepatitis virus in blood extend beyond those involved in blood and plasma transfusion. The multiple opportunities for exposure to hepatitis virus of this origin are not generally recognized, the diagnosis frequently is not entertained in the absence of a history of transfusion, and some opportunities for prevention occasionally may be overlooked. It seems desirable, therefore, to cite some of the many potential sources of infection from blood:

1. *Purposeful parenteral introduction of blood or its products:*
   - (*a*) Transfusions of blood, plasma, or serum.
   - (*b*) Passive immunization with normal or convalescent blood, plasma, or serum.
   - (*c*) Incorporation of plasma or serum into other biological products.
   - (*d*) Therapeutic local application of blood or its products to open lesions.
   - (*e*) Injection of certain products of human plasma fractionation.
2. *Accidental parenteral or oral introduction of blood or its products:*
   - (*a*) Inadequately sterilized syringes, needles, lancets, and other instruments that come in contact with blood or its products and are used for:
     1. Intravenous, intramuscular, subcutaneous and intracutaneous injections (diagnostic, therapeutic and prophylactic procedures).
     2. Venous punctures for blood withdrawal only.
     3. Skin punctures (blood counts, other blood specimens, etc.)
   - (*b*) Contamination of open skin and mucous membrane lesions or accidental ingestion of blood or its products through handling of blood specimens or blood-contaminated materials (excreta, wound discharges, etc.).

Contributing to the importance of the above sources is the fact that either IH or SH type virus may be present in blood and either the oral or parenteral route of entry therefore may be involved. Also pertinent to these considerations is the fact that in any infectious disease in which minute amounts of blood contain the agent, the possibility of mechanical or biological transmission by biting insects cannot be excluded. Although no definite evidence of transmission by biting insects has been obtained to date, a previously un-

reported observation is of some interest in relation to this question.[14] In 1945, an effort was made by the author and Dr. Joseph Stokes, Jr., in collaboration with Lt. William Jahnes, to obtain experimental evidence of mechanical or biological transmission of hepatitis virus by biting insects. A group of mosquitoes was allowed to feed alternately on a volunteer who was in the preicteric stage of experimentally induced virus IH hepatitis and a "normal" volunteer. The same mosquitoes subsequently were allowed to feed on three other volunteers after intervals of one, two, and four weeks. None of these volunteers developed definite evidence of hepatitis during the ensuing six months, although one of the group on which the mosquitoes fed after one to four weeks developed minor abnormalities with certain hepatic tests. These findings were not considered sufficiently distinctive to warrant a diagnosis of hepatitis. However, on subsequent oral challenge inoculation with known active virus IH, he proved to be resistant to infection. This tempts one to suggest the possibility that this man had been infected originally by the mosquitoes and had been immunized by subclinical infection. In retrospect, it is unfortunate that this mosquito experiment was conducted with our strain of virus IH as later studies showed that this virus was effective in inducing overt hepatitis with jaundice in only one of the nine volunteers injected by the parenteral route [3] although most of them apparently experienced a subclinical immunizing infection. Repetition of this experiment with virus SH, which was highly effective in inducing overt hepatitis when injected parenterally, would appear to deserve a high priority among future studies. The equivocal result of the study mentioned, if not coincidental, raises many interesting questions. Such a mechanism of transmission would provide a very tenable explanation for one of the epidemiologic mysteries associated with virus SH, namely, the mechanism for its natural perpetuation and survival prior to the development of man-made mechanisms for its dissemination.

Thus, it is possible that there are few persons who may not have had opportunities for exposure to blood borne hepatitis virus through one or another of these potential mechanisms.

While on this aspect of the subject, the increasing *medicolegal importance* of blood transmitted hepatitis virus warrants special comment. This matter has arisen because of the relationship between homologous serum hepatitis and certain indispensable technics of routine medical practice. In particular, the purposeful injection of blood and certain of its products involves a hepatitis risk which must be weighed against the existing indications for such injections. Attention to the preventable mechanisms of transmission which have been cited under the "accidental" mechanisms also is important in this respect. The unfortunate experience of an Italian physician recently described in a letter written by a foreign correspondent in Italy and published in the foreign correspondence section of the J.A.M.A.[15] illustrates this point:

"After a trial of more than one month and a verdict elaborated in sixteen hours, as reported in a previous letter, the physician of Varese who had been accused of disseminating by his imperfect technic an epidemic of 'syringe hepatitis' was sentenced to serve five years in prison, to discontinue practice for two additional years and to compensate the families of the victims, of whom 12 had died and an additional 100 were infected. The entire nation has been interested. The sentence seems terrible, for in 1946 nobody in Italy knew anything about infection with hematogenous hepatitis through imperfect sterilization of the syringe. The physician of Varese gave no less than 50 intravenous injections of a tonic to his patients every day.

"The trial had aroused the entire medical profession in Italy because the incriminated physician had an excellent reputation. The defense council will apply to the Court of Appeal, but for the moment the physician, who had enjoyed liberty conditionally, has been imprisoned."

Although it seems doubtful, on the basis of the evidence described, that the action taken in this case was justified, it serves to indicate the potential hazard involved.

As questions concerning the *control* of blood borne hepatitis virus frequently arise, it has seemed worthwhile to consider what preventive measures may be taken, on the basis of existing knowledge, in order to reduce the incidence of infections from this source.

I. *Detection of Infected Donors:* Such a preventive measure obviously would be of great value if it could be accomplished. Unfortunately, no practical method for rapid demonstration of hepatitis virus in blood has yet been developed. However, it appears that some infectious donors may present detectable evidence of clinical or subclinical hepatic injury. Such donors might be recognized by the routine performance of a relatively small group of laboratory tests. For this purpose, the following scheme is suggested:

1. Exclude donors with history of hepatitis or unexplained recent symptoms.
2. Physical examination with particular reference to liver.
3. Screening tests for hepatic disturbance:

   a. Before blood is drawn:

   1. Urine bilirubin.
   2. Urine urobilinogen (sensitive simple methods are available).
   3. Exclude donor if either test positive.

   b. After blood is drawn but before blood is released:

   1. Total and prompt direct reacting serum bilirubin.
   2. Cephalin cholesterol flocculation test (24 hr.).
   3. Thymol turbidity and flocculation tests.
   4. Do not release blood if any of these tests positive.

All professional donors periodically should have a careful "hepatic" history, a physical examination, and a bromsulfalein test in addition to the above group of tests.

Questions that are frequently asked are whether and when it is safe to use blood from a donor who has recovered from acute hepatitis. No evidence available to date permits an answer to these questions. It is not yet known whether viremia persists or recurs intermittently following acute hepatitis. Thus, the length of the various time intervals that have been adopted by certain blood banks as the minimum period that must elapse before acceptance of such donors is not based on factual evidence and merely represents an attempt to take a reasonable precaution. It would seem more logical, in the absence of definite knowledge concerning this point, to exclude as donors all persons known to have had this disease.

II. *Inactivation of Hepatitis Virus in Blood and Blood Products:* Until some method for detecting hepatitis virus in blood and its products becomes available, it will not be possible to solve this problem by exclusion of infected units. Even with the employment of the methods of donor selection suggested above, carriers who have no history of apparent infection and present no laboratory indications of hepatic disturbance must be presumed to exist and will escape detection. Therefore, the main hope in this field of prevention lies in the development of some method for inactivation of hepatitis virus in blood and its products. The resistance of hepatitis viruses to methods or conditions which inactivate or eliminate many pathogens makes this a formidable problem as most procedures that are capable of inactivating hepatitis virus also are injurious to blood and plasma. In an effort to find some solution to this problem, Oliphant first suggested in 1944 the possible usefulness of ultraviolet irradiation of plasma for inactivation of hepatitis virus in plasma.[16] Since that time, substantial improvements have been made in the technics for irradiation of plasma. Studies by Hampil and Spizizen, in the Sharp and Dohme Laboratories, demonstrated the effectiveness of this procedure in inactivating certain other viruses in plasma.[17] In collaboration with these workers, Blanchard, Stokes, and Wade recently have provided evidence that this method was effective in inactivating one strain of virus SH in plasma.[17] It would appear, therefore, that carefully controlled ultraviolet irradiation of plasma may provide one means of decreasing the incidence of this disease. It should be pointed out, however, that only one strain of hepatitis virus has been tested to date and that this was not a highly potent strain. Additional confirmatory studies thus are urgently needed before ultraviolet irradiated plasma can be accepted as free from the risk of viable hepatitis virus. Even if subsequent studies establish its effectiveness, ultraviolet irradiation is not a convenient or desirable solution to this problem, as the technical difficulties involved are substantial, its use must be restricted to centers where special equipment and technical experts are available, and the present technic is not applicable to whole blood. A more generally useful method is needed and the most

promising hopes for this originate from recent observations which suggest that some viruses may be destroyed by small quantities of certain chemical agents which can be added to blood or plasma without serious alterations of these substances or danger to the human recipient of materials so treated.[18]

III. *Prevention of the Disease in Recipients of Blood and Its Products:* The ability of human immune serum (gamma) globulin to prevent virus IH hepatitis when injected in the incubation period prior to the onset of the disease was demonstrated in 1944 by Dr. Joseph Stokes, Jr. and the author.[1, 19] Its effectiveness has since been confirmed by other investigators in four additional epidemics occurring in widely separated areas both in this country and abroad,[1, 2] the most recent confirmation being provided by Drs. John Farquhar and Joseph Stokes, Jr. in an institutional epidemic occurring in 1948.[6] These investigators also obtained some evidence through this same study which suggested that persons who received gamma globulin during the incubation period, or were exposed shortly after receiving gamma globulin, experienced an inapparent infection which resulted in active immunization.[20] That such immunization can occur from subclinical infection has been demonstrated experimentally in studies previously reported by the author in connection with Dr. Sidney S. Gellis and Dr. Joseph Stokes, Jr.[3] In this study, volunteers who failed to develop clinically detectable signs of active infection after parenteral inoculation with virus IH were subsequently found to be resistant to oral challenge inoculation with highly active virus IH. The possibility of accomplishing active immunization by a proper combination of gamma globulin and attenuated hepatitis virus has been suggested by Dr. Stokes and this deserves prompt exploration and study.[20]

Unfortunately, the usefulness of human immune serum globulin in the prevention of virus IH infections apparently does not extend to virus SH infections,[21] which appear to be the most frequent problem associated with blood or plasma transmission. Although the studies to date indicate that even large and repeated doses of gamma globulin fail to prevent virus SH hepatitis, the fact that some blood transmitted infections are due to virus IH probably warrants the use of prophylactic injections of gamma globulin in association with multiple transfusions of blood and non-irradiated plasma. This also appears desirable as a prophylactic measure in recognized exposures occurring through the "accidental" mechanisms. In this respect, it seems desirable to emphasize the fact that careful follow-up studies of several thousand persons injected with gamma globulin have failed to reveal any evidence that this material itself has been a source of either virus IH or SH infections.[21]

IV. *Reduction of Incidence by Selection of Materials:* It is evident from the foregoing that none of the methods of prevention thus far described can be depended upon to eliminate the hazard of viral hepatitis at present inherent in the use of blood and certain of its products. Gamma globulin

and the currently used heat treated human serum albumin solutions apparently can be regarded as free from this risk.[22] The data described above indicate that the risk of hepatitis is greater with some blood products than with others and suggest that a reduction in incidence may be accomplished by limiting, as much as possible, the use of those associated with greater risk.

When indications and availability permit, the choice of materials for transfusion might be based on the following tentative plan:

1. *Minimal risk:*
   - *a.* Human serum albumin solution (heat treated).
   - *b.* Ultraviolet irradiated plasma???
2. *Small risk:*
   - *a.* Whole blood and single plasma units.
3. *Moderate risk:*
   - *a.* Small plasma pools.
   - *b.* Multiple transfusions of whole blood or single plasma units.
4. *Maximal risk:*
   - *a.* Large plasma pools.

The exact place of irradiated plasma in this list is uncertain. As this method usually is applied only to relatively large plasma pools and its consistent effectiveness has not been demonstrated, it does not seem wise to promote its widespread use until additional information becomes available. Recent studies by Janeway and his associates indicating that the antihemophilic fraction of blood plasma has been a source of hepatitis virus have been cited elsewhere.[21]

V. *Prevention of "Accidental Mechanisms" of Transmission:* The prevention of certain of the "accidental mechanisms" described above obviously is possible but involves difficult and costly changes in certain everyday medical technics. Reliable information concerning the frequency of transmission by these mechanisms is not available. However, sound epidemiological evidence of transmission by improperly sterilized syringes and needles exists[23, 24] and the hazard therefore must be recognized. Until it becomes possible to prove that the frequency is so small as to be negligible, it would seem that no choice exists concerning recommendations in this matter and that individual properly sterilized syringes, needles, and other instruments that penetrate the skin should be used for each patient.

As information concerning the effect on the hepatitis viruses of various methods of sterilization is lacking, it is difficult to define "adequate" sterilization in respect to this problem. The available experimental evidence bearing on this point is as follows[1]:

1. Hepatitis virus in serum albumin solution was inactivated by heating at 60° C. for 10 hours.

2. Hepatitis virus in contaminated water was inactivated by "breakpoint" chlorination.

Neither of these studies provided information concerning the minimal requirements for inactivation of the virus by either method but they do indicate the susceptibility of hepatitis virus to inactivation by proper exposure to heat and chemicals. Obviously the presence of blood clots and other foreign materials tends to interfere with exposure of the hepatitis virus to disinfecting agents. Thus, proper and thorough cleansing of syringes, needles, and other instruments is of primary importance. If this is well done, it is probable that complete immersion in boiling water for five minutes would represent "adequate" sterilization. Likewise, if care is taken to insure complete contact of all surfaces of thoroughly cleansed syringes, needles, lancets, etc. with potent chemical disinfectants for at least one hour, it seems reasonable to assume that "adequate" sterilization would result. In my opinion, however, heat sterilization should be employed whenever possible and the autoclave would be the method of choice.

Prevention of infection from contact with blood or blood contaminated materials or objects involves precautions of such magnitude that special measures other than reasonable care appear justifiable only in respect to patients with recognized or suspected hepatitis.

Summary and Conclusion

"Viral hepatitis" is presented as a syndrome caused by at least two, primarily hepatotropic, filterable, infectious agents (Viruses IH and SH) which have not yet been associated with specific serological responses but which produce, as their outstanding manifestation, evidences of liver injury, with or without phenomena suggestion an infectious origin. Some of the major advances in knowledge concerning etiology, epidemiology, clinical aspects, and prevention are enumerated and certain of the remaining problems are discussed. The possible relationship of hepatitis viruses to certain etiologically obscure types of hepatic disease and the possible rôle of virus SH in the etiology of so-called sporadic hepatitis are considered. The problems associated with blood transmission of hepatitis viruses are reviewed and possible methods of reducing the incidence of infections from this source are considered. The data presented herein clearly indicate that many important aspects of the problem of viral hepatitis remain to be solved.

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THE CLINICAL MANIFESTATIONS AND LABORATORY DIAGNOSIS OF RICKETTSIALPOX *

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RICKETTSIALPOX, the newest member of the human rickettsioses, was first observed in 1946 [1, 2] and thus far has been confined exclusively to the metropolitan area of New York City. The etiological agent was identified by Huebner and his associates [3] as *Rickettsia akari*, a new species which is serologically related to the spotted fever group of rickettsiae. The disease is apparently transmitted to man by a blood-sucking mite, *Allodermanyssus sanguineus*, an arthropod parasite of rodents.[4] *Rickettsia akari* has been isolated from pools of these mites collected in dwellings where cases of rickettsialpox have recently occurred. The tropical rat mite, *Liponyssus bacoti*, has also been shown experimentally to be a potential vector,[5] although its rôle in the natural transmission of the disease is undetermined at the moment. An animal reservoir of the infection exists in the common house mouse, *Mus musculus*,[6] and the associated occurrence of rickettsialpox with the rodent infestation of dwellings has been well established.[7]

Rickettsialpox continues to be seen frequently in New York City, especially in upper Manhattan and the Bronx, although only a few cases have occurred in Brooklyn and none have been recognized on Staten Island. In the past three years nearly 500 cases have been reported to the Bureau of Preventable Diseases, New York City Department of Health,[8] and many others have undoubtedly escaped recognition, especially those of mild or atypical character. Since the spring of 1947, 35 proved cases of rickettsialpox have been seen at the Columbia-Presbyterian Medical Center of which 22 were admitted to the hospital and 13 were followed in the out-patient department. These cases furnish the basis for the present communication, which deals with the clinical manifestations of the disease and the methods employed in the laboratory for specific serologic diagnosis and for the isolation of the responsible agent. Brief reference is also made to the results of treatment with aureomycin in two patients and with streptomycin in one patient.

CLINICAL MANIFESTATIONS

The general clinical features of rickettsialpox have been previously described.[9] The onset of the illness is usually characterized by the appearance of a primary cutaneous lesion at the site of inoculation by the arthropod vector. About a week later the patient develops fever, chills, malaise and

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headache, followed shortly by a secondary papulovesicular cutaneous eruption which may resemble the rash of varicella. Although the constitutional symptoms may be severe and prolonged for a week or more, the disease is benign and no deaths have occurred.

The common course of the disease may be illustrated by the following brief case report:

The patient was a 50 year old white female who entered the hospital on May 6, 1948, complaining of fever, headache, malaise and a cutaneous eruption of one week's duration. Two weeks before admission she first noticed a small papular lesion on the inner aspect of the right upper arm. This lesion became progressively larger during the next few days. About a week later she began to experience alternate sensations of chilliness and heat, and found her oral temperature to be 102°. At the same time she developed an increasingly severe frontal headache, a slight non-productive cough and malaise. Five days before admission she noted the appearance of a generalized skin eruption. In the interim the temperature continued to fluctuate between 102° and 104°, the headache persisted and she experienced several shaking chills. On entrance to the hospital she did not appear acutely ill. The temperature was 101.6°, pulse 80, respirations 18 and arterial pressure 130 mm. Hg systolic and 80 diastolic. A rash was present over the face, trunk and extremities consisting of widely spaced erythematous papules from 2 to 4 millimeters in diameter, most of which showed small vesicles at their summits. On the inner surface of the right arm, just above the elbow, there was an erythematous lesion about 1.0 centimeter in diameter with a central blackish crust. The eruption was neither painful nor pruritic. The conjunctivae were clear. There were no petechiae. One vesicular lesion was seen on the soft palate just to the left of the midline. A few enlarged, slightly tender lymph nodes were palpated in the right axilla, but otherwise there was no lymphadenopathy. The lungs were clear. The heart was not remarkable. The abdomen was negative and the spleen was not enlarged.

The laboratory findings were as follows: Hemoglobin 15.0 grams, erythrocyte count 4,300,000, leukocyte count 4,240 with polymorphonuclears 58 per cent, lymphocytes 38 per cent, monocytes 2 per cent and eosinophiles 2 per cent. No abnormal leukocytes were seen in the smear. The urinalysis, Kline test and chest roentgen-ray were negative. The erythrocyte sedimentation rate (Westergren method) was 26 millimeters in one hour.

The patient's course in the hospital was uneventful. The temperature fell to normal in 36 hours, the rash rapidly faded and she was discharged on the morning of the fourth day.

The rickettsialpox complement fixation test on a sample of blood collected on the day of admission was negative. The test was positive in a serum dilution of 1–32 on a specimen of blood taken three weeks later.

Incubation Period. The incubation period of rickettsialpox has not been well established. One patient developed fever nine days after an apparently single exposure to a known focus of an infection.[1] In another individual who acquired the infection accidentally in the laboratory, the exact time of a single exposure was known.[10] This person developed a primary lesion on the seventh day, fever on the tenth day and a secondary eruption on the twelfth day after exposure. The interval between the time of infection and the appearance of the systemic reaction thus may be 9 or 10 days, although both shorter and longer periods of incubation probably occur.

Age and Sex Incidence. As in most infectious diseases which are unrelated to occupation, rickettsialpox has no predilection for either sex. In the present series of 35 cases, 18 were females and 17 were males. The ages of the patients ranged from two to 56 years.

Eighteen of the 35 cases occurred in persons of the negro race, a much larger proportion than would be expected among general admissions to this hospital. The high incidence among colored patients is probably a reflection of their economic status and the fact that their living quarters are usually poor and often heavily infested with mice.

Primary Lesion. In 29 of the 35 patients primary cutaneous lesions could be readily identified. These consisted of areas of erythema and in-

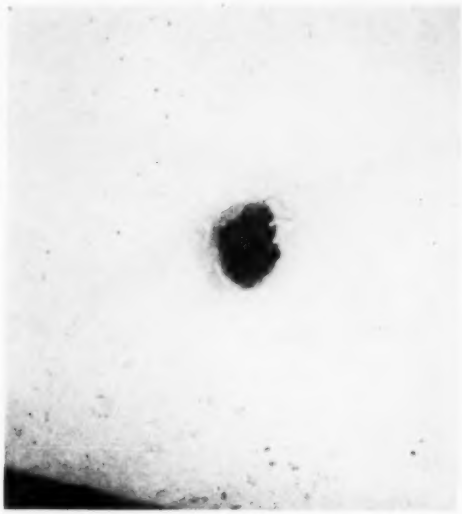

FIG. 1. A typical late primary lesion. This lesion was situated on the right upper arm of a 15-year-old boy.

duration from 1.0 to 2.5 centimeters in diameter. At an early stage the lesions exhibited a central vesicle containing slightly cloudy or opaque fluid. In older lesions this vesicle had ruptured or undergone desiccation, leaving a dark brown or black crust which closely resembled the primary eschar described in fievre boutonneuse, tsutsugamushi disease, and occasionally in cases of Rocky Mountain spotted fever. The lesion was slightly painful and tender in a few instances, but usually it produced no local symptoms and in several cases it had not been previously recognized by the patient. A typical late primary lesion is shown in figure 1.

Twelve patients had single primary lesions on either the arms or legs. The head or neck was the site in eight others, in one of whom it was situated

just inside the right nostril. This latter individual had contracted the infection accidentally in the laboratory. Four other patients showed lesions on the back, buttock and penis. In the remaining five patients *two* primary lesions were observed and were distributed as follows: forehead and cheek; forehead and abdomen; forehead and leg; chest and axilla; and two close together on the thigh, which are illustrated in figure 2. In almost every instance the lymph nodes draining the areas where the primaries were situated were enlarged and slightly tender, but although this local lymphadenopathy was often striking in its magnitude there was never any evidence of lymphangitis.

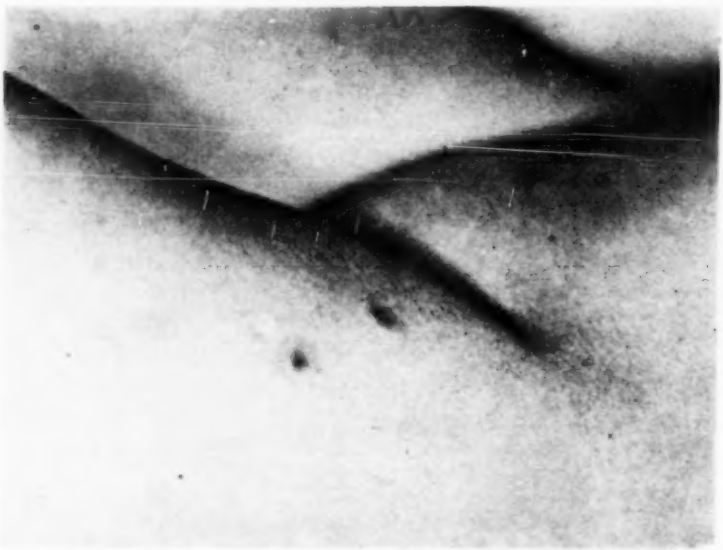

FIG. 2. Two primary lesions situated close together on the thigh of a two-year-old girl.

Cutaneous Eruption. The cutaneous eruption of rickettsialpox appeared from a few hours up to a week after the onset of the febrile period of the disease. In the majority of cases, however, it developed within 72 hours after the temperature became elevated, and most commonly on the second day of fever. The individual lesions varied considerably in their appearance but usually consisted of erythematous maculo-papular areas ranging from 2 to 10 millimeters in diameter (figure 3). They were discrete and generally distributed over the body surface, including the face, and in three cases they were observed on the palms and soles. In several patients the rash was either so faint, or the lesions were so sparse, as to be almost inapparent. In one patient the rash was indistinguishable from that seen in murine typhus.

The outstanding feature of the individual lesion in most cases was the development of vesiculation, although it is important to point out that occasionally no vesiculation whatever was seen. In a number of instances the vesicles appeared only as small, pin-point, opaque areas at the summits of papules. More frequently, however, the vesicles were larger and often con-

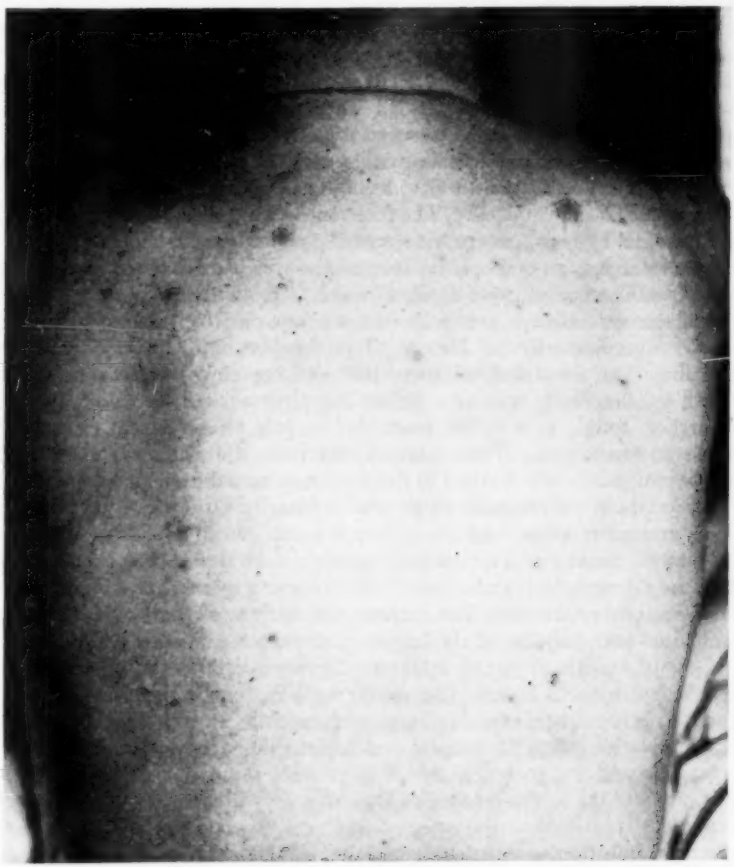

FIG. 3. The typical secondary eruption of rickettsialpox in a 34-year-old man.

stituted the majority of the papule, being surrounded by a band of erythema. These latter vesicles were difficult to distinguish individually from those seen in chickenpox. The eruption was pruritic in several cases although in most patients it did not cause any discomfort and was never painful. As the eruption retrogressed blackish crusts formed at the sites of the larger vesicles.

These later became detached, leaving areas of brownish pigmentation, but residual scarring was never noticed.

In nine of the 35 cases an enanthem was seen on the mucous membranes of the oral cavity, usually on the palate. The lesions resembled those seen on the body surface but were usually more transient, sometimes being visible for less than 48 hours. The enanthem may be missed unless it is searched for at daily intervals, and it is probable that the incidence is higher than recorded in this series of patients.

Symptoms and Physical Signs. The chief constitutional symptoms were fever, headache, and malaise, which were present in every case. These symptoms appeared from two to seven days after the patient first noted the presence of the primary cutaneous lesion. The maximum temperature ranged from as low as 100.2° F. to as high as 105.6° F., the majority being between 102° F. and 104° F. The fever curve was of the remittent type and fell to normal by lysis, generally toward the end of the first week.

Headache was an outstanding feature and was usually severe and located in the frontal area. In two cases, however, it was mainly occipital.

Malaise was always present, often accompanied by backache and generalized muscular aching. Nearly all of the patients complained of chilly sensations and about half of them had shaking chills, sometimes accompanied by drenching sweats. Other symptoms noted occasionally were rhinorrhea, cough, sore throat, photophobia, pain on movement of the eyes, nausea and vomiting. Four patients had pain and stiffness of the neck, which were sufficiently marked in three of them to warrant lumbar puncture.

On physical examination there was ordinarily little to be found except the cutaneous eruption and the primary lesion, when present. As previously noted, the regional lymph nodes draining the site of the primary lesion were usually enlarged and tender. However, a generalized lymphadenopathy was observed in only five patients and in none of these was it striking. The spleen was palpable at the height of the disease in four patients and a mild conjunctivitis appeared in three others. Examination of the cardiovascular system was invariably negative and only one patient, an infant two years of age, had signs of pulmonary involvement. In this patient the physical examination revealed dullness and moist râles over the left lower chest posteriorly and the roentgen-ray findings were compatible with a bronchopneumonia of the left lower lobe. Unfortunately it could not be determined with certainty whether the pneumonitis was directly associated with the rickettsial infection or whether some other etiological agent was responsible.

Laboratory Diagnosis

The routine laboratory examinations regularly failed to disclose anything of note with the exception of the total and differential leukocyte counts. Counts were done in 28 of the 35 cases and in 21 of these there was a moderate or marked leukopenia during the acute phase of the illness with cells

ranging between 2,500 and 5,500 per cubic millimeter. Five patients had total counts from 6,000 to 10,000 and two patients had a slight leukocytosis, the maximum being 12,500 cells. The differential count was essentially normal in 22 patients and no abnormal leukocytes were seen in the stained smear. In six individuals, however, the smears showed a number of abnormal leukocytes—large mononuclear cells with vacuolated cytoplasm—similar to the peculiar cells usually seen in the blood of patients with infectious mononucleosis. Indeed, three of these patients were admitted to the hospital with a provisional diagnosis of infectious mononucleosis based in part on the hematological findings. The abnormal mononuclear cells did not tend to persist in the blood and were present for only a day or two; their significance is undetermined. Tests for heterophile antibody never showed a significantly elevated titer of sheep cell agglutinins, either during the acute illness or in convalescence.

Rickettsialpox is similar to Q fever, among the group of rickettsial infections, in that the Weil-Felix reaction is negative. Agglutinative tests with Proteus OX19 and OXK were done with the acute and convalescent phase serums of 13 patients and in no instance was a positive result obtained although low titers of agglutinins were observed in a few cases.

The serums of a number of patients were also tested for cold agglutinins against Group O human erythrocytes and in none were the titers significantly elevated.

Examinations of the cerebrospinal fluid in the three patients previously referred to were completely negative.

Specific Serologic Diagnosis. In recent years serologic methods have been developed for the precise diagnosis of rickettsial infections. The method most widely employed is the complement fixation test, using antigens prepared from rickettsiae grown in the yolk sacs of chick embryos. One type of antigen consists of washed, concentrated rickettsial suspensions from which the chick tissue has been largely removed by flocculation and differential centrifugation.[11] Another type is the soluble antigen which is released into the aqueous phase when saline suspensions of infected yolk sacs are shaken with ether.[12] This soluble antigen gives specific reactions, is easy to prepare and can be obtained from all species of rickettsiae except *Coxiella burneti*, the causative agent of Q fever.[13] In performing complement fixation tests for diagnosis the principle adhered to, if possible, is simultaneously to test two serums, one obtained in the acute phase of the illness and the other in convalescence, from two to six weeks later. The demonstration of the appearance of antibody, or of a significant rise in antibody titer, in the convalescent serum, establishes the temporal relationship of the specific immune response to the illness and thereby enables a retrospective diagnosis to be made. If no acute phase serum has been obtained, as in cases where the patient is first seen after the disease has subsided, the examination of a convalescent specimen alone may still give information of diagnostic value.

Complement fixation tests were carried out with acute and convalescent phase serums from all patients in this series, with the exception of two from whom no convalescent specimens could be obtained. The antigens were of the soluble type, prepared from *R. akari* grown in chick embryos, together with similar antigens obtained from the rickettsiae of murine typhus and Rocky Mountain spotted fever.* Serial doubling dilutions of the sera ranging from 1–8 to 1–256 were tested by a modified Kolmer technic, using two exact units of complement in the system. The period of fixation was usually one hour at 37° C., since good results were obtained under these conditions and the anti-complementary properties of the serums and antigens were much less of a problem than when fixation overnight at 4° C. was used. Some of the serums, however, were tested by the latter fixation method.

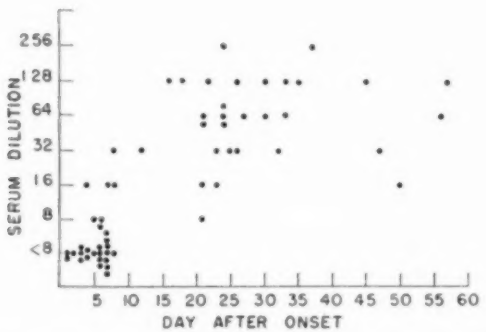

FIG. 4. A composite record of the results of complement fixation tests with rickettsialpox antigen at intervals following the onset of the disease.

Positive results were recorded as the highest dilutions of the serums that gave at least 2 plus fixation with the various antigens.

The composite results of the complement fixation tests with rickettsialpox antigen are shown in figure 4. In every case tests revealed the development of specific antibody and thereby confirmed the clinical diagnosis. A considerable degree of cross reaction was observed with the rickettsialpox and spotted fever antigens indicating a close antigenic relationship between *R. akari* and *R. rickettsii*. Indeed, in some patients the complement fixation reactions were more strongly positive with spotted fever antigen than with rickettsialpox antigen, an observation which has also been reported by Huebner and his associates.[3] In addition, minor cross reactions were observed occasionally with murine typhus antigen. These findings are illustrated in table 1, which shows some representative results of complement

* The murine typhus and Rocky Mountain spotted fever antigens were generously supplied by Dr. Herald R. Cox, Director, Section of Viral and Rickettsial Research, Lederle Laboratories, Pearl River, New York.

fixation tests with all three antigens. The serological relationships of *R. akari* are of great interest and are under further study at the present time.

Complement fixation tests were also done on the serums of three patients collected 9, 10 and 15 months, respectively, after infection. Moderately elevated titers of antibody were still demonstrable in each instance, indicating that the immune response is of fairly long duration, a phenomenon that has been shown to occur in other rickettsial diseases such as murine typhus [14] and Q fever.[15] The persistence of detectable antibody for many months after all clinical signs of the disease have subsided is of some practical significance in attempting to make a long-range retrospective diagnosis in certain cases.

TABLE I

Cross Reactions in Complement Fixation Tests with Serums of Cases of Rickettsialpox

Case	Day after Onset	Rickettsialpox Antigen	Spotted Fever Antigen	Murine Typhus Antigen
R. S.	6	0	0	0
	24	64*	64	0
E. M.	7	0	0	0
	45	128	32	8
H. R.	1	0	0	0
	24	64	128	16
L. W.	4	16	0	0
	30	64	16	8
L. A.	6	0	0	0
	21	64	128	0
A. W.	8	16	32	16
	26	128	64	16
A. J.	4	0	8	0
	12	16	32	0
H. S.	6	0	0	0
	37	256	32	0

* Figures are reciprocals of the highest serum dilutions giving at least 2 + fixation with the respective antigens.

Isolation of the Etiological Agent. Attempts were made to recover the etiological agent in 10 patients by inoculating blood collected early in the disease intraperitoneally into mice, guinea pigs and into the yolk sac of chick embryos. From eight of these patients *R. akari* was isolated in the mice and from one individual the organism was also isolated directly in chick embryos. No primary isolations were successful in guinea pigs. The method employed was to inject a group of 8 to 10 Swiss mice each intraperitoneally with 0.5 to 1.0 c.c. of defibrinated blood freshly collected from the patient. Blood clot triturated with sterile bacteriological broth also proved to be a satisfactory inoculum. If animals were not immediately

available the blood was frozen and stored in a cabinet refrigerated with solid carbon dioxide. We have isolated rickettsiae from such specimens at intervals up to six months after storage.

Deaths were rarely observed in infected mice following primary inoculation, but in the second week after injection the animals often appeared ill and exhibited lethargy, ruffled fur, labored breathing and anorexia. Not infrequently, however, infected mice appeared to be perfectly healthy. Regardless of their external appearance the animals were sacrificed from seven to 10 days after inoculation and examined for inguinal and axillary lymphadenopathy, increased amounts of peritoneal fluid, and hypertrophy and congestion of the spleen and liver. Any or all of these signs were found to

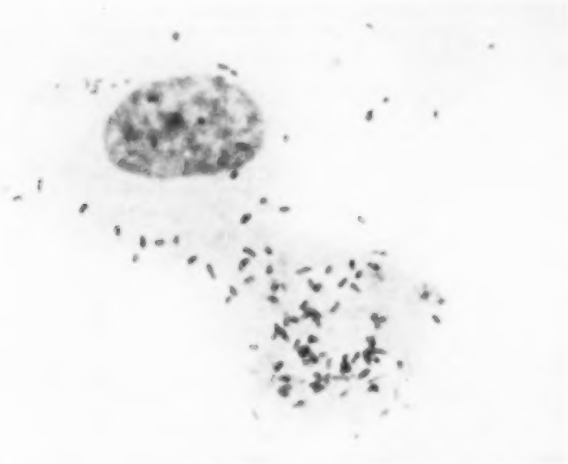

FIG. 5. *Rickettsia akari* in a smear of the peritoneal fluid of an infected mouse. Stained by Macchiavello's method. Note rickettsiae in the nucleus as well as in the cytoplasm of the cell. Many of the organisms are extracellular.

denote infection and rickettsiae could be easily demonstrated in smears of the spleen, liver and intraperitoneal fluid stained by the Macchiavello method. The organisms were observed lying extracellularly as well as within both the cytoplasm and the nucleus of parasitized mononuclear cells (figure 5).

The accumulation of peritoneal fluid was often striking and occasionally exceeded 2.0 c.c. in mice weighing between 15 and 20 grams.

Subsequent passage of suspensions of infected liver and spleen to fresh mice usually resulted in a fatal illness, the animals dying from 5 to 10 days after inoculation, depending on the size of the inoculum, with typical findings at autopsy. Among the eight strains of *R. akari* isolated in this manner, to date, serial passage in mice has shown some to be of relatively low

virulence while others are highly pathogenic with LD50 titers exceeding 10^{-5}.

From infected mice on the primary or later passages, *R. akari* were readily transferred to chick embryos. Suspensions of liver and spleen were inoculated into the yolk sacs of seven day old embryos which were then incubated at 35° C. The embryos died from four to nine days later, depending on the size of the inoculum, and numerous rickettsiae were demonstrated in the smears of the yolk sacs stained by the Macchiavello method. Once established, the strains could be maintained indefinitely in chick embryos by serial passage. Studies of one strain have shown that its pathogenicity for mice remained unimpaired through six consecutive transfers in eggs.

Treatment

Rickettsialpox is a non-fatal disease and therefore the need for specific therapy is not as urgent as it is for other rickettsial infections such as typhus and spotted fever. Nevertheless, the unmodified infection may cause severe constitutional symptoms and the patient may be acutely and uncomfortably ill for a few days to a week or more. Certain antibiotics, including streptomycin,[16] chloromycetin [17] and aureomycin [18] have been shown to exercise a rickettsiostatic effect in chick embryos and experimental animals, while both aureomycin and chloromycetin have recently been demonstrated to have a remarkable therapeutic action in human rickettsial infections.[19] We have treated one case of rickettsialpox with streptomycin in a dosage of 0.5 gm. every six hours, but the drug apparently failed to influence the natural course of the disease. More recently, two patients were treated early in the disease with aureomycin in a dose of 1.0 gm. every six hours by mouth. In each of these cases the temperature fell precipitously to normal within 24 hours, accompanied by a rapid defervescence of symptoms and fading of the cutaneous eruption. The results of aureomycin therapy in human infections with *R. akari* will be reported in more detail elsewhere.

Summary

Rickettsialpox is a novel rickettsial infection of relatively mild character which thus far has not been observed beyond the environs of New York City.

The clinical and laboratory features of the disease have been described together with means for specific serologic diagnosis and isolation of the etiological agent.

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PULMONARY EMBOLISM: ITS INCIDENCE AT NECROPSY IN RELATION TO PERIPHERAL THROMBOSIS *

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The most dangerous complication of venous thrombosis is pulmonary embolism, with its mortality of about 20 per cent.[1] Such embolism has been reported by Barnes [3] to be responsible for 34,000 deaths in this country each year. Knauer [2] has reported fatal pulmonary embolism in 2.5 per cent of 33,558 autopsies. Hunter [4] found that over 50 per cent of older people confined to bed evidenced thrombosis of the deep leg veins, with pulmonary emboli from these veins accounting for over 3 per cent of all deaths.

The factors which determine whether a thrombus will or will not embolize are not fully understood. It is commonly assumed that the incidence of pulmonary embolism in any given age or disease group is a direct function of the incidence of thrombosis. If this were not so, the nature of the disorders with an altered frequency of embolization might serve as a clue to the understanding of embolization. Accordingly, a study was undertaken to determine if disease of any particular system enhanced or retarded the embolization of thrombi. This postmortem study was further stimulated by the clinical impression that the incidence of peripheral thrombosis and pulmonary embolism was surprisingly low at Goldwater Memorial Hospital. This hospital consists largely of elderly, chronically bed-ridden patients who might be considered likely candidates for more frequent thromboembolic disease.

Material: In this study, the postmortem incidence of embolism and thrombosis in various disease and age groups was compared. The necropsy protocols of 516 cases were studied. The first 202 of these were consecutive cases consisting of 67 females and 135 males ranging in age from 18 to 89. As will become evident in the analysis of the data, the diagnosis of Laennec's cirrhosis assumed a singular rôle. Therefore, an additional 79 consecutive autopsy protocols in which there was a final diagnosis of Laennec's (portal) cirrhosis were selected for further study. In addition, 217 non-cirrhosis protocols of selected age groups were also reviewed.

Analysis of Data

Table 1 showed the incidence of thrombosis to be comparatively low in the age group below 50. In the age groups beyond 50, thrombi were

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From the Third (New York University) Division, Goldwater Memorial Hospital, Welfare Island, New York 17, N. Y., and the Department of Medicine, New York University College of Medicine, New York, N. Y.

found with a frequency twice as high as in the younger group.* When analyzed by individual decades, no significant variation was found. Pulmonary emboli, on the other hand, manifested a marked statistical increase beyond 70 years of age. It should be noted that while the incidence of arteriosclerosis in the age group 60 to 69 was equivalent to that found in the older decades, the incidence of pulmonary embolism was considerably less. As was anticipated, the incidence of arteriosclerosis was found to rise sharply until age 60. Beyond this age, the incidence was too high to permit useful comparison by decades.

In table 2 the data were correlated with the pathologist's final diagnosis. Cardiac thrombosis was found with greatest frequency (28 per cent) in the cardiovascular group and peripheral thrombosis was noted in 20 per cent of the 101 cases comprising this group. In the 18 patients constituting the hepatic disease group, cardiac thrombosis occurred in five cases and periph-

TABLE I

Age	Total Number of Cases	Thrombi	Pulmonary Emboli	Atherosclerosis
Under 50	20	3 15%	1 5%	10 50%
50–59	32	11 34%	1 3%	24 72%
60–69	56	21 41%	5 9%	52 93%
70–79	58	21 40%	11 21%	56 96%
80–89	36	12 36%	8 23%	33 92%

eral thrombosis in two cases. Pulmonary embolism occurred in from 10 to 20 per cent of all disease groups with the startling exception of cases of portal cirrhosis. In the 18 cases of portal cirrhosis, there was not one instance of pulmonary embolism. No extrapulmonary embolus was discovered in the hepatic disease group with the possible exception of one doubtful case. In no other disease group analyzed were emboli so totally lacking.

The failure to demonstrate emboli in the patients with liver disease led us to examine the autopsy protocols of other cases bearing a final diagnosis of Laennec's cirrhosis. Seventy-nine additional consecutive cases of Laennec's cirrhosis examined at autopsy were analyzed. In 17 of the 79

* This report is based on autopsies conducted according to the routine established in the laboratory. It is probable that if special dissections of the lower limbs were made the incidence of peripheral thrombosis would be higher than is recorded in this paper. Nevertheless, since the necropsies were all performed according to the same technic, a comparison of incidence in the different groups is valid. In each case dissection of the pulmonary arteries was carried out in the same routine manner.

cases, cardiac thrombi were found. Peripheral thrombosis was present in nine cases. This compares favorably with the figures obtained among the 18 cases of liver disease presented in table 2. In one case, a non-embolic thrombus was discovered in the pulmonary artery but again we failed to find

TABLE II

Disease Group		Total Number of Cases	Incidence of					
			Thrombosis		Embolism			Atherosclerosis
			Cardiac	Peripheral	Pulmonary	Other	Doubtful	
Cardiovascular	Number	101	38	20	15	20	2	92
	Per cent		38%	20%	15%	20%	2%	92%
Hepatic	Number	18	5	2			1	14
	Per cent		28%	11%			6%	77%
Renal	Number	29	4	3	4	3	1	25
	Per cent		14%	10%	14%	10%	4%	88%
Respiratory	Number	51	6	3	5	4	2	45
	Per cent		12%	6%	10%	8%	4%	90%
Neurological	Number	46	6	6	9	5	1	38
	Per cent		13%	13%	20%	11%	2%	84%
Malignancy	Number	45	5	7	6	6		35
	Per cent		11%	16%	13%	13%		71%
Additional Cases of Hepatic Disease								
Hepatic	Number	79	17	9	0	1	0	16
	Per cent		21%	11%		5%		80%

a single instance of pulmonary embolism in the 79 cases of portal cirrhosis. One case revealed an extrapulmonary embolus. Combining the 18 cases presented in table 2 with the additional 79 of table 3 we find that in 97 cases of portal cirrhosis no pulmonary emboli were uncovered.

DISCUSSION

It is the common belief that thrombosis and embolism are parallel phenomena. Our data reveal two significant findings which fail to support this concept: (1) The absence of pulmonary embolization in 97 cases of cirrhosis of the liver regardless of age group, and (2) A sharp increase in the incidence of emboli to the lungs in patients after 70 years of age. In both groups peripheral thrombosis was found with about equal frequency.

The conditions responsible for the development of intravascular thrombosis appear to be inadequate to explain the variable incidence of pulmonary thromboembolism as revealed by the above data. The blood coagulation

mechanism is usually disturbed in chronic liver disease.[5] It is unlikely that the prothrombin time delay frequently seen in cirrhosis of the liver could inhibit embolization without preventing peripheral thrombosis. In the older age groups the blood has also been found to be hypocoagulable [8] and liver function tests in the aged have frequently been demonstrated to be abnormal even in the absence of clinically demonstrable liver disease.[5] Nevertheless the data show a striking increase in the incidence of pulmonary thromboembolism beyond 70 years of age. We are led to conclude, therefore, that factors other than simple hypocoagulability may influence the incidence of pulmonary embolism.

This belief is strengthened further by the observation that certain cases of the migratory type of thrombophlebitis seem almost never to yield emboli while others clinically indistinguishable from the former variety, are frequently accompanied by pulmonary embolization. The first type of migratory thrombophlebitis may continue for many months, manifesting frequent fresh lesions without endangering the host with emboli to the lungs.[6] In the latter, pulmonary embolism may occur with startling frequency during the course of the disease.[7] These two types can be further distinguished by their response to anticoagulants. The embolizing type can be controlled by adequate anticoagulant therapy while the non-embolizing type sometimes cannot.

Summary and Conclusions

In 184 consecutive miscellaneous cases, excluding liver disease, the incidence at necropsy of pulmonary embolism was 14 per cent.

In 97 instances of portal cirrhosis, no pulmonary emboli were found. The incidence of cardiac and peripheral venous thrombosis in these 97 cases of liver disease was not significantly different from that of the miscellaneous group.

Since decreased coagulability of the blood is accompanied by reduced embolization in some instances (cirrhosis of the liver) and by increased embolization in other instances (aged patients), factors other than changes in coagulability of blood must be sought to explain the occurrence of pulmonary embolism.

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CHEST X-RAY SURVEYS IN GENERAL HOSPITALS, A CRITICAL REVIEW *

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ROENTGENOGRAPHIC chest surveys of general hospital populations are fairly recent innovations. In 1936, Hodges [4] reported a chest x-ray survey of 1101 admissions to the University of Michigan Hospital. He found roentgen evidence of intrathoracic lesions in 90, or 8.1 per cent of those patients. Examination of their subsequent hospital records revealed 14 instances in which pulmonary pathology found on the survey films had not been recognized clinically. This represented an incidence of 1.5 per cent. Also in 1936, Pohle et al.[8] reported 1460 hospital admissions with normal lungs on physical examination. In 34, or 2.3 per cent of this group, x-ray evidence of pulmonary tuberculosis was present, and in four, or 0.3 per cent, active reinfection tuberculosis was suspected. In 1940, Plunkett and Mikol [7] reported x-raying 4853 admissions to 14 general hospitals in upstate New York and in 128, or 2.6 per cent, evidence of reinfection tuberculosis was found. No clinical data were presented in this series.

During the past 10 years, marked technical improvements have made available a miniature chest photofluorographic technic which was widely used by induction centers, the armed services, and large industrial plants during the war. With this background of previous experience, the United States Public Health Service and local health agencies have sponsored mass chest surveys in various localities throughout the United States.

The first report in the literature on the use of photofluorography in hospital surveys appeared in 1941. Douglas and Birkelo [2] reported examining 4727 prospective mothers on 4 by 5 film. In 29, or 0.61 per cent, roentgen evidence of active tuberculosis was discovered.

The first use of photofluorography as a *routine* hospital procedure appeared in April, 1942, when Hodges [5] analyzed 7841 patients admitted to the University of Michigan Hospital during a four month period. He found that 732, or 9.3 per cent, required more comprehensive x-ray study. Again there was no report of clinical follow-up on the group.

In 1945, Scatchard and Duszynski [9] reported the results of a chest survey made on 1832 admissions to the Edward J. Myer Memorial Hospital of Buffalo during the two and one-half summer months of 1944. Of these, 36, or 1.4 per cent, were found to have previously unsuspected pulmonary tuberculosis. Ten of the 36 cases had either been x-rayed previously and found negative or had not been x-rayed on previous admissions. The remaining 26 had never before been seen at the hospital. Further, in 1107 of these

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patients previously known to the hospital, the prevalence of unsuspected tuberculosis was 1.1 per cent in contrast to a prevalence of 3.6 per cent in the 725 individuals admitted without ever having had previous contact with the institution. These authors give suggestions for a suitable installation and stress the importance of having the unit operate between 6 p.m. and 10 p.m.

Hanser and Dundon [3] in 1945 reported the examination at the University Hospital in Cleveland of 1000 asymptomatic hospital employees on both 14 by 17 and 4 by 5 films. Twenty-one minimal lesions of pulmonary tuberculosis were found, an incidence of 2.1 per cent, and four errors were made in the first reading of the miniature films.

The American Hospital Association [1] in coöperation with the United States Public Health Service and the National Tuberculosis Association advocates for all patients entering clinics and hospitals the routine use of chest x-rays as a service comparable to the routine blood Wassermann examination.

In 1946, W. P. Shepard, the President of the National Tuberculosis Association, commented as follows: "No well run hospital would admit a case of typhoid fever without instituting proper isolation. Today tuberculosis is more common than typhoid fever, it is more elusive, often unrecognized, and is contagious. Admitted unknowingly, it is a menace to the patient, hospital personnel, other patients, and the public. Admitted knowingly, it is easy to isolate, the patient's proper care is assured, and the public is protected. Routine chest x-rays of all admissions is a feasible and practical procedure."

In the monograph, "The Management of Tuberculosis in General Hospitals," published in 1946 by the Council on Professional Practice of the American Hospital Association, it is stated that in new hospital admissions "residual signs of inactive tuberculous lung infection are seen in 10–20 per cent" while "significant tuberculosis (reinfection type) has been found in 1.5 to 4.3 per cent."

Little information can be gleaned as to follow-up procedure and ultimate results in these hospital surveys. No follow-up study of a hospital x-ray survey was found in the literature. However, Peterson,[6] in 1946, reported a one year hospital survey in which all new admissions to the Minneapolis General Hospital had been Mantoux tested. Positive reactors had been x-rayed and those with significant findings had been carefully followed. The present neglect of follow-up planning is reflected in the absence from the literature of appropriate emphasis on this essential aspect of survey work.

In December, 1947, an effort was made to study the current effectiveness of hospital surveys in the Philadelphia area. An analysis was undertaken of the four 70 mm. photofluorographic units operating at Philadelphia General Hospital and at three teaching hospitals—Temple, Jefferson, and Hahnemann. These four units were analyzed with the following points in mind: (1) location of the unit, (2) its lay-out, (3) procedure, (4) staff, (5) record-keeping, and (6) follow-up.

1. *Location.* Three of the four units were well located adjacent to receiving wards. The fourth unit was adjacent to the entrance for private patients and visitors.

2. *Lay-out.* Not one of the four units had a suitable lay-out. All four had inadequate space and none had a waiting room. Two units had no dressing rooms, one unit had two, both of which were poorly ventilated, and the fourth had three cubicles. Only one unit had its own developing room and that room was so small that the dryer had to be placed where it interfered with the free access of patients and technicians to the unit itself. It is apparent that these survey units had been set up in odd available space rather than as carefully planned adjuncts to the admission departments.

3. *Procedure.* No adequate system insured that all admissions report to the unit, but arrangements at one hospital were such that no patient was discharged without having received a photofluorogram. Two units arranged for the technicians to receive a daily list of admissions against which that day's photofluorograms were checked. An effort was then made to have those missed on admission report to the unit. However, by the time this list reached the wards, some of the cases were unable to be moved. No unit operated around the clock nor over week ends. No unit operated on definite shifts to cover evening admissions.

Photofluorograms were developed and read daily at three of the four units. Reports from these units were promptly appended to hospital charts. At the other unit, the system was uncertain, the impression being gained that film rolls were cut when sufficient exposures had been made and read when some member of the x-ray department could be found who was not too busy to read them.

Film-reading was done at one unit by a part-time certified roentgenologist reading daily the films taken the previous day. At a second unit four Fellows in Roentgenology took turns at daily film-reading. Films at the other two units were read by any one of the roentgenologists available at the time the films were developed. At one unit reports were sent to the wards within 24 hours of the film-reading. At a second unit the photofluorograms were stapled to the reports and these sent to the wards promptly. At neither of the other two units was there a definite system though one of these made a charge of $1.00 per photofluorogram for both private and ward patients. The roentgenologist in charge of this unit explained that ward cases could receive reductions in this as in other charges by consulting the Social Service Department. No other unit made any charge for photofluorographic services.

4. *Staff.* The largest hospital, with 53 average daily admissions, had two full-time registered technicians and a full-time clerk operating the unit, a clerk and a secretary full-time at the unit office, a nurse and a nursing supervisor full-time for follow-up, a certified roentgenologist part-time for daily film-reading, and a part-time chest specialist as supervisor.

The next best staffed unit was in a hospital with 37.5 average daily admissions. It had one full-time unregistered technician and a second registered technician part-time. This unit was under the supervision of a Fellow in Roentgenology, as were the remaining two.

A third unit, in a hospital with 45 average daily admissions, alternated technicians from the x-ray department.

The fourth unit was operated by a stenographer who had been trained to take films. In her absence, the hospital doorman took them. This hospital had 35 average daily admissions.

There was no other personnel for record-keeping or follow-up at any of the last three described units.

5. *Record-keeping.* At the largest of the four hospitals, a master file was kept in which there was available a report on every x-ray ever taken. In addition, a "significant" file was maintained in which duplicate I.B.M. cards were filed with the 70 mm. photofluorograms and their readings plus follow-up correspondence. A ledger was maintained in which all significant cases were entered. It provided space for a five-year follow-up on each. The nurses kept a chronological file for follow-up of these cases.

At a second unit a ledger was kept in which daily entries were made of names, type of film taken, 70 mm. reading and subsequent 14 by 17 reading. However, no further follow-up was maintained. This unit also had a master file and a duplicate file of significant cases.

The other two units maintained no record-keeping system whatever so that there was no information available as to the number of photofluorograms taken on admissions. The roentgenologist in charge of one of these units "thinks" that 80 per cent of the photofluorograms were taken on out-patients. At the other unit, the resident "guessed" that a total of 20 to 30 individuals per day were processed.

No unit had available data on the time interval between admission and photofluorography and none kept a running record of percentage of admissions x-rayed.

6. *Follow-up.* Only one unit maintained a staff for follow-up of cases. At this institution two full-time nurses and one part-time chest specialist were kept busy. Hospital charts were examined and diagnostic procedures checked. Where data were inadequate the responsible service was notified. Because personnel was insufficient, emphasis was placed on those cases read as "probably active," and while this program was theoretically excellent, in practice the patient had often left the hospital before follow-up revealed inadequate clinical studies. However, at this unit the inadequacies were recognized and a definite effort is being made to correct the shortcomings. No statistical report is yet available from this unit on the number of tuberculous admissions to wards other than the tuberculosis ward.

One of the other units made an analysis in January, 1948, of photofluorograms taken over a six-month period. This analysis was based on 14 by 17 retakes only. Of the 8992 individuals x-rayed at this photofluoro-

graphic station, 14 by 17 retakes were subsequently made on 416 of the 1257 individuals read as having significant survey findings and on 261 of the 7442 negative cases. The study revealed that, of the 261 cases read "negative" by survey who incidentally had subsequent 14 by 17 films, 50, or 19.1 per cent, had pathology. Of these 50, only 23 of the retakes were chronologically sufficiently close to the survey film to be considered survey errors. Of the 416 retakes on survey cases thought to reveal significant pathology, the survey impression was confirmed in 290 and altered in 126. There was no organized clinical follow-up.

As far as could be determined no follow-up procedures were in practice at the remaining two units.

Discussion

Although hospital surveys are widely advocated, it appears that their ultimate purpose and fundamental philosophy are not clearly appreciated. The primary purpose of hospital chest surveys is not diagnostic, but is the detection of infectious tuberculosis in order to protect hospital personnel and other patients. This achievement is accomplished only by prompt diagnosis with isolation and appropriate treatment of cases uncovered by survey. If properly conducted, surveys of this type become an important adjunct to the tuberculosis control program of the community.

The concept of surveys as screening processes is of the greatest importance. Such a concept suggests that a significant percentage of cases whose films are read as "probably tuberculous" should ultimately prove to be non-tuberculous. No film should be read as revealing non-tuberculous pathology in a patient who is subsequently proved to have tuberculosis. This is one way of stating that a properly read hospital survey should be "overread" from the viewpoint of tuberculosis. Such an approach requires considerable indoctrination of survey film readers.

If hospital surveys are to be effective, a very high percentage of patients must report for photofluorography *at admission*. It is obvious that x-ray at discharge cannot protect contacts and often does not even lead to accurate diagnosis and therapy for the patient himself, viz. the following case report:

> A 37-year-old white female, a private patient admitted in active labor March 31, 1947, received a 70 mm. photofluorogram at discharge 10 days post-partum. The film was read as revealing bilateral tuberculosis. The report was sent to her obstetrician who advised the patient to consult a chest specialist. The patient failed to follow this advice. On February 9, 1948, ten months post-partum, a 14 by 17 film taken because of 102° temperature, emaciation, dyspnea, etc., revealed far advanced tuberculosis with bilateral giant cavitation and soft infiltrations throughout the balance of both lungs. The baby was found to have an active tuberculosis at the right base, the husband to have a minimal lesion of indeterminate activity and a maid's film was read as suspect.

This case of active tuberculosis had been in the Maternity Division for 10 days undiagnosed and unisolated. Photofluorography at discharge had

not assisted in the protection of hospital personnel nor contacts. It did not provide a reason for clinical study which would have resulted in diagnosis. Had a positive sputum been obtained during hospitalization, the case would have been reported to the Municipal Division of Tuberculosis and follow-up would have been assured.

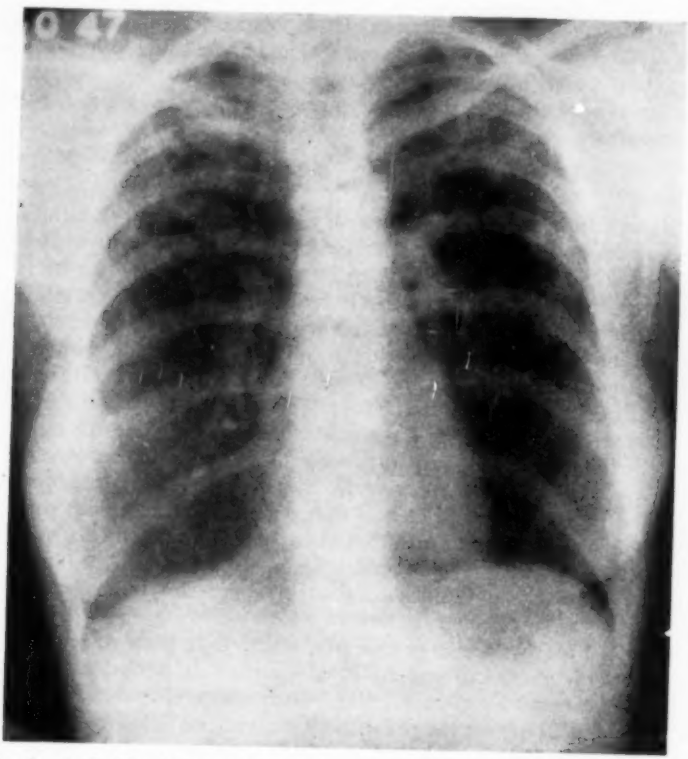

FIG. 1. A. G., 37, white female, a private patient admitted in active labor on March 31, 1947, received a 70 mm. photofluorogram on April 10, 1947, at discharge 10 days post-partum which revealed moderately advanced tuberculosis with infiltrations upper halves of both lung fields.

It is apparent that some types of patients cannot be x-rayed on admission —women admitted in active labor, critically ill patients, certain accident cases, children too young, and psychotic patients too disturbed to coöperate. However, the hazards presented by such patients can be minimized by a suitable routine.

An analysis of admissions at the largest of the four hospitals revealed the fact that about 50 per cent of admissions were made during hours when the

unit was not in operation. At this hospital, during October, 1947, 1011 individuals were admitted during hours when the unit was closed. Of these 495 were too ill to report to the unit at the time they were subsequently sent for. This suggests that an important reason for failure to x-ray all admissions lies in the fact that the unit was not open around the clock.

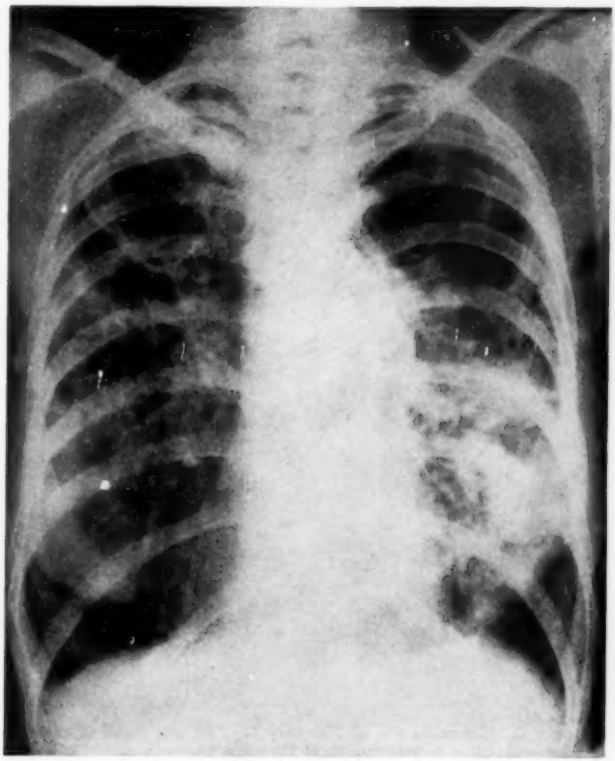

FIG. 2. A. G., on February 9, 1948, ten months post-partum, a 14 by 17 film taken because of 102° temperature, emaciation, dyspnea, etc., revealed far advanced tuberculosis with bilateral giant cavitation and soft infiltrations throughout balance of both lungs.

One of the four units had a satisfactory follow-up program but even this was not fully effective in actual practice. It is obvious that, in the setting up of these four units, provision was made primarily for the taking and reporting of films. Record-keeping was seriously inadequate at all four units so that it was not possible to evaluate the real service rendered by these units to their respective hospitals and to the community.

Recommendations

1. Photofluorographic surveys in general hospitals should be inaugurated as part of an integrated hospital tuberculosis control program rather than as ends in themselves. While the taking and reading of photofluorograms quite rightly belongs under the jurisdiction of the X-ray Department, the follow-up belongs under the Department of Chest Diseases.

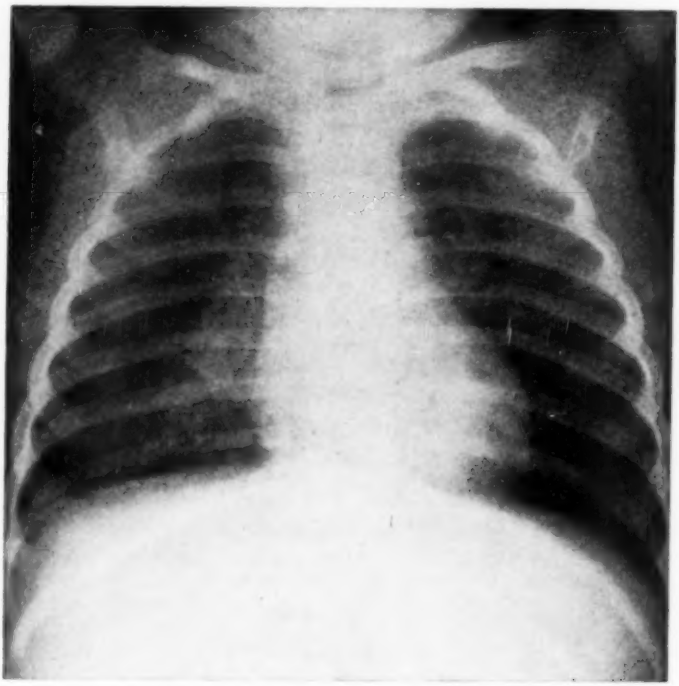

Fig. 3. Baby G., 10 months old, on February 12, 1948 was found to have an active tuberculosis at the right base.

2. The taking, processing, reading and reporting of photofluorograms should be carried out within 24 hours. However, these procedures represent only the beginning of the survey work. A follow-up staff—medical, nursing, secretarial, and social service—is as necessary to an effective hospital chest survey as are the photofluorographic unit, developing room, technician, and roentgenologist. Provision for such personnel should be made when the program is set up.

3. A periodic check is necessary to be sure that all patients are being referred for photofluorograms. Responsibility for referral of admissions

and out-patients to the unit should be placed at the admission desk and the central Out-Patient Department registration desk. Some device for conspicuous marking of admission and clinic cards should be used in order that no patient be admitted to the ward, private room, or to a clinic without having received a photofluorogram. At the most successful unit studied such a

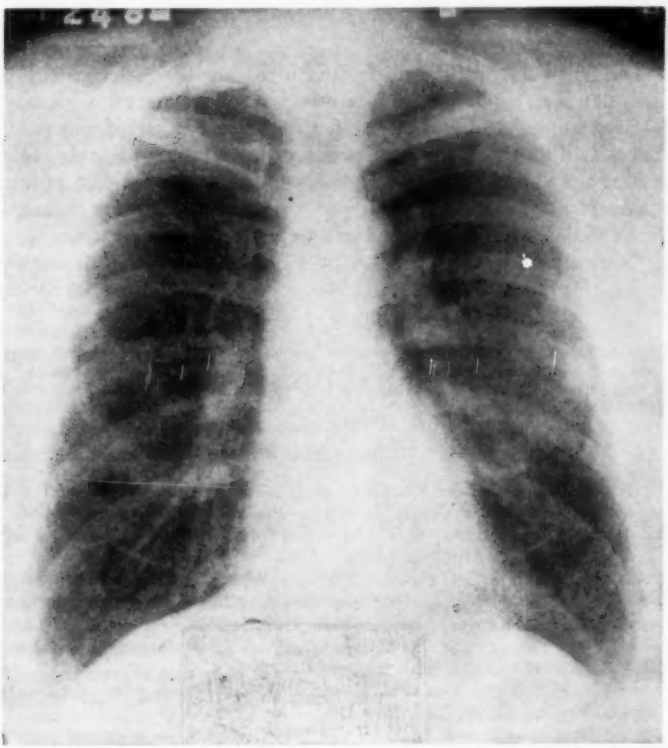

FIG. 4. C. G., the husband, on February 12, 1948 was found to have a minimal lesion of indeterminate activity at the left apex and first interspace.

device consisted of a 3.5″ by 4.25″ hollow "X" stamped in bright green directly over the admission or clinic card. This does not interfere with reading the data over which it is stamped.

4. Provision should be made for the taking of photofluorograms around the clock seven days a week. It is not necessary that a registered technician be on duty nights and weekends. A system should be set up for inclusion within the program of those patients who cannot be x-rayed on admission:

a. Prenatal cases and individuals scheduled for operations of election should be referred to the unit before admission.

b. Accident cases, patients having had emergency operations and children too young to coöperate should be sent via stretcher to the regular x-ray department.

c. Those cases too ill to have had photofluorograms or x-rays in the regular department should have special studies for tubercle bacilli if sputum be available.

5. The hospital office should be instructed not to discharge any patient who has not had a photofluorogram. However, constant vigilance must be exercised to obviate the necessity for referring any significant percentage of patients at discharge. The uncovering of tuberculosis at this point does not protect the patient nor his hospital contacts. Good public health practice makes it mandatory that proper follow-up be assured on these patients as well as those surveyed on admission or during hospitalization.

6. Correlation of subsequent clinical reports with survey findings should be routine and prompt, providing a valuable source of material for medical and nursing teaching.

Note: Since the preparation of this paper, the authors have become increasingly aware of the value of chest surveys as case-finding procedures for pulmonary neoplasms. Awareness of this aspect significantly enhances the contribution made by routine x-raying of hospital populations.

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CASE REPORTS

DEATH DUE TO PARATHION, AN ANTICHOLINESTERASE INSECTICIDE *

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The introduction in recent years of anticholinesterase (antiChE) compounds as insecticides has led to problems arising from their toxicity for man. The antiChE compound most widely used at the present time is parathion (p-nitrophenyl diethyl thionophosphate).[1] This anticholinesterase was introduced by the Germans and is now manufactured in this country, chiefly for use as an insecticide in agriculture, under such names as "Geigy Parathion," "Lethalaire G-54 Parathion Aerosol," "Chipman Parathion," "P. A. R. Parathion," "Phos Kit Parathion," "Paradust Parathion," "Dow Parathion," "Vapophos Parathion," "Penphos Parathion," "Aphamite Parathion," "Parathion Insecticides," "Genithion Parathion," "Edco 15 Parathion," and "Niran (Parathion)." Studies performed following the administration of parathion to experimental animals have shown that most of the pharmacological properties of this compound can be explained in terms of its antiChE action.[2, 3]

Detailed studies of the effects in man of other esters of phosphoric and pyrophosphoric acid which are potent antiChE agents, such as di-isopropyl fluorophosphate (DFP) and tetraethyl pyrophosphate (TEPP, which is also employed as an insecticide), have shown that these esters produce muscarine-like, nicotine-like, and central nervous system effects.[4–8] Because the inhibition of cholinesterase (ChE) enzymes by DFP is irreversible, and by TEPP and parathion only partly reversible, the effects of these compounds are prolonged and cumulative. Until the ChE enzymes of the tissues have been restored, subjects who have been exposed to these compounds remain susceptible to the effects of any subsequent exposure, which may be by any route, including absorption from the skin, respiratory tract, conjunctivae, gastrointestinal tract, or following injection.

The following case report is that of a man who died after repeated exposure to the insecticide, parathion, and who manifested the characteristic cholinergic symptoms and changes in ChE activity attributable to an antiChE agent.

Case Report

A. N., a white male aged 35, was employed as a mixer of liquid parathion (97 per cent pure) and ataclay (a clay powder) to produce a clay dust with parathion

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Work was performed in part under a contract between the Medical Division, Chemical Corps, U. S. Army, and the Johns Hopkins University.
From the Department of Medicine, Johns Hopkins University and Hospital, the Department of Surgery, Mercy Hospital, and the Office of the Chief Medical Examiner, Baltimore, Maryland.

adsorbed in concentration varying from 15 to 34 per cent. The resulting product is marketed and is used as an insecticide after dilution with clay to 1 to 2 per cent, or with water to 0.06 per cent, parathion. This work exposed the patient to liquid parathion and to parathion adsorbed on ataclay. He had been employed from February 21 through March 11, April 21 and 22, and from May 2 through May 6. He wore a carbon filter respirator, protective goggles, rubber gauntlets, hip length rubber boots, rubber apron, and protective coveralls, which did not, however, completely cover the arms and neck. There is no indication that he had any symptoms prior to May 6. On May 6 the concentration of parathion in the ataclay was increased from 25 to 34 per cent. (The saturation point of parathion on ataclay under standard conditions is approximately 40 per cent.) On the same day there was an increase in the atmospheric temperature and humidity. The patient worked from 3 p.m. to 7:30 p.m., when he stopped to have supper. He removed all his protective clothing except the boots and washed his hands thoroughly. The dining room and food were in a separate part of the plant from that in which parathion was handled. At 8 p.m., 10 minutes after eating, he became nauseated and then had the desire to defecate. Before he could reach the toilet, he developed abdominal cramps accompanied by vomiting, tenesmus and involuntary defecation. This continued during the next half hour, during which the patient also began to have profuse sweating, constant giddiness, headache, blurring of vision, restlessness, and anxiety. Muscular fasciculations appeared in the tongue and eyelids, and there was some generalized muscular weakness.

He was admitted to the hospital two hours after the onset of symptoms. Physical examination revealed a well developed 35 year old white man who had walked into the hospital despite moderately acute distress from the symptoms described above. He was tense, anxious, and tremulous, but rational and well oriented. He was sweating profusely, and there was excessive salivation. Speech was somewhat slurred. There was some difficulty forming words, and repetition of the last word or syllable. The pupils were pin-point, and the fundi could not be seen. Respirations were normal, at 16 per minute, and the lungs were clear. The heart was normal to percussion and auscultation. The pulse rate was 92 per minute, and the blood pressure 152/96 mm. of mercury. (The preëmployment blood pressure had been 100/70, on February 20.) On admission, muscular fasciculations were observed in the tongue and eyelids, and there were irregular jerking movements of the eyes. Shortly afterward the muscular fasciculations became generalized and were very marked. There was a moderate degree of generalized muscular weakness. Tendon reflexes were normal, and there were no abnormal reflexes. No abnormality of sensation was detected.

Forty minutes after admission, the patient gradually lapsed into coma. Tendon reflexes and response to painful stimuli disappeared. Following the development of coma, repeated generalized convulsions occurred. Between convulsions the respiration was Cheyne-Stokes, except when a mixture of 5 per cent carbon dioxide and 95 per cent oxygen was administered. There was no gross evidence of bronchoconstriction, but there did appear to be excessive bronchial secretion. Otherwise the lungs remained clear. The blood pressure rose from 152/96 to 186/100. There was no evident anoxia or carbon dioxide retention to account for this rise in the blood pressure. There was frequent urinary and rectal incontinence, with watery stools. Gastric aspiration yielded 500 c.c. of brownish fluid having the mercaptan-like odor of parathion.

One pin-point pupil was slowly and incompletely dilated by the local instillation of one drop of 1 per cent atropine sulfate every 15 minutes for one hour. Examination of the fundus at that time revealed moderate elevation of the optic disc of about 2 diopters. Half an hour later the pupil returned to pin-point size, and the fundus could no longer be visualized.

The patient was treated with atropine sulfate, 0.6 mg. being injected intramuscularly four times during the first hour. This resulted in diminution of the excessive sweating, salivation, and bronchial secretion. Two hours later he received another injection of 0.6 mg. atropine sulfate. He was given a continuous infusion of saline and glucose. During his first convulsion he was given 140 units of curare intravenously over a period of three minutes. This diminished the severity of the convulsive movements, but did not prevent their recurrence. The curare immediately abolished the muscular fasciculations. He was given a second injection of curare (100 units) about half an hour after the first injection.

The patient remained comatose and areflexic for four hours. Then, seven hours after the onset of symptoms, he began to respond again to painful stimuli, and tendon reflexes could again be elicited. The pupils became less pin-point, and some response to light was obtained. Coincident with this improvement the blood pressure gradually fell from 186/100 to 150/80. One hour after the return of reflexes and of response to painful stimuli the patient regained consciousness, spoke a few words and appeared to be rational and oriented. He stated that vision in both eyes was blurred, and that he had difficulty focussing. During the next two hours he appeared to be improving gradually, becoming more alert and speaking more easily. However, shortly thereafter, 10 hours after the onset of symptoms, respiration became shallow, rapid, and labored, and the pulse unobtainable. Fifteen minutes after this change was noted the patient died.

Autopsy Findings

Postmortem examination, performed four hours after death, revealed only diffuse vascular engorgement throughout the body, with widespread capillary dilatation, edema, and hyperemia of all the organs, including the lungs, liver, spleen, kidneys, and brain. The brain was edematous, and there was an increased amount of clear cerebrospinal fluid in the ventricles and subarachnoid space, as well as a "pressure cone." There was a slightly increased amount of mucus in the trachea and bronchi. These findings are in general similar to those that were observed after a death attributable to neostigmine methylsulfate.[9]

Table I

Comparison between the ChE activity of various tissues of patient A. N., and the average activity of four subjects who had received no exposure to any anticholinesterase agent and who were autopsied a similar length of time after death due to other causes. The ChE activity is expressed in millimoles of acetylcholine bromide hydrolyzed per minute per gram of tissue per ml. Determinations were made manometrically.[4]

	Cholinesterase Activity		
	Control Average	A. N.	A. N.
	mM ACH Br $\times 10^{-3}$		% of Control Average
Plasma	9.9	0.5	5
Red blood cells	14.0	1.7	12
Liver	3.5	1.5	43
Kidney	2.2	0.9	41
Cerebral cortex	4.8	0.6	12
Thalamus	34.0	12.3	36
Cerebellum	13.1	6.2	47
Pons	7.5	2.4	32
Medulla	3.6	1.2	30

Determination of Cholinesterase Activity

During the four hours between the time of death and autopsy the body was kept in a refrigerator at 5° C. Determination of the ChE activity of the various tissues was performed four days after the autopsy. During the intervening time the tissues were kept in a refrigerator at 5° C. The ChE activity of the plasma and red blood cells was markedly depressed to 5 and 12 per cent of normal activity. The ChE activity of the liver, kidney and various parts of the brain was also depressed below normal, but, except for the cerebral cortex, the depression was not of the same degree as that of the plasma and red blood cells (table 1). This difference may be due to more rapid restoration of the ChE enzymes of the tissues than of the plasma and red blood cells during the interval between the last exposure to parathion and death. This is suggested by the partial clinical improvement which the patient showed during the three hours prior to death, and by the reported occurrence in experimental animals of delayed death due to parathion, after an initial partial improvement and some restoration of ChE activity of the tissues.[2]

Analysis for Parathion

Chemical analysis for parathion was performed on the organs removed at autopsy. The procedure used was that of Averell and Norris[10] as modified by Lehman.[11] The modifications involved preliminary drying of the tissues with anhydrous sodium sulfate and subsequent extraction with ether in a Soxhlet extraction apparatus. The ether was evaporated by a stream of air at room temperature and the residue taken up with ethyl alcohol and water and reduced according to the method of Averell and Norris. Control tissues were analyzed at the same time and correction made for these blank values. The results of these analyses, expressed as micrograms of parathion per 100 grams of tissue, were: liver, 148 micrograms; brain, 139 micrograms; kidney, 169 micrograms.

Discussion

Studies on the effects of related antiChE esters (DFP and TEPP) in man have shown that the slow rate of restoration of ChE enzymes in the tissues following depression by these esters is an important factor in their production of severe cumulative effects.[4-8] The ChE activity of the plasma, red blood cells, and tissues could be considerably reduced without the appearance of cholinergic symptoms, but a further reduction below the level compatible with normal function resulted in marked symptoms.

Examination of the plasma and red blood cells of patient A. N.'s fellow employees, who had had varying degrees of exposure to parathion, revealed that most of them had some depression of ChE activity.[12] Those with more marked depression of ChE activity also had characteristic cholinergic symptoms, while those with lesser degrees of depression of ChE activity had no symptoms. It is very probable that patient A. N. had had some depression of ChE activity of his blood and tissues prior to his last exposure to parathion. On this day, the increased concentration of parathion in the ataclay, and the increased atmospheric temperature and humidity, apparently resulted in a further absorption of parathion, and a depression of ChE activity of the tissues below the level compatible with life.

Following the occurrence of this death due to exposure to parathion, employees at the chemical company in which the death occurred have received periodic determinations of plasma and red blood cell ChE activity, in order to detect those employees who have absorbed this compound.[12] Employees with reduced ChE activity of the plasma or red blood cells have been removed from all exposure to parathion until the ChE activity returned to normal, over a period of several weeks. It is strongly urged that this procedure, as well as all possible safety measures to reduce the degree of exposure and of absorption, be used in any installation or situation in which there is exposure to an antiChE compound, whether in the production, packaging, handling, or spraying of these compounds, in the harvesting of fruits or vegetables on which they have been sprayed, or in their ingestion on insufficiently weathered fruits or vegetables.

The treatment of the effects of excessive exposure or overdose of antiChE compounds relies chiefly on atropine. This may be administered in very large doses in such a situation, as high as 2 to 3 mg. intramuscularly every hour as long as cholinergic symptoms are present, since the tolerance for atropine is greatly increased by the action of the antiChE compound.[8] It is probable that the patient described above should have received larger amounts of atropine than were administered. Other therapeutic measures include washing the skin and gastric lavage to remove any unabsorbed antiChE compound, parenteral replacement of fluids, and administration of oxygen. If muscular weakness is marked and involves the muscles of respiration, intubation and mechanical aid to respiration may become necessary. The administration of curare results in the cessation of muscular fasciculations, but since an overdose may cause weakness of the muscles of respiration, its use is probably not advisable.

Summary

A report has been presented of a man who died following repeated exposure to the antiChE insecticide, parathion. Safety measures to reduce exposure and absorption, and periodic determinations of plasma and red blood cell ChE activity, are strongly recommended for all persons exposed to this, or any related, antiChE compound.

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HEPATOSPLENOMEGALY AND LIVER DAMAGE IN GRAVES' DISEASE *

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Liver damage as a consequence of thyrotoxicosis is well known. Since the association was first mentioned by Paul [1] in 1865, a considerable literature has developed on the subject. Numerous authors [2–17] have called attention to the occurrence of clinical jaundice as a somewhat rare but by no means unknown concomitant of thyrotoxicosis. In some of these reports [2, 7, 8] the course was that of an acute hepatitis with recovery, in others [3, 12, 13] jaundice did not recede until after successful removal of the inciting toxic thyroid gland, and in others [9, 10, 11, 14, 17] the course was that of an acute yellow atrophy with death. Most writers have agreed that the presence of jaundice is a serious prognostic sign when it occurs in the course of thyrotoxicosis.

To discover lesser degrees of hepatic damage numerous clinical studies of liver function have been done employing the entire galaxy of available tests. Among these have been such standard liver function tests as the oral and intravenous hippuric acid test,[18–24] galactose tolerance test,[25–29] bromsulfalein retention,[30, 31] prothrombin time,[32] total protein and A/G ratio,[33] blood cholesterol levels,[34] glucose tolerance curves,[35] and the Takata-Ara test.[36] In addition, studies have been made employing the phenoltetrachlorphthalein retention test,[37] the cinchophen oxidation test,[38] and the estimation of the blood amylase level [39] as indicators of liver function. The newest of the liver function tests, the excretion of benzoyl glucuronate,[40] has already been employed in the evaluation of hepatic function in thyrotoxicosis. All of these studies have uniformly demon-

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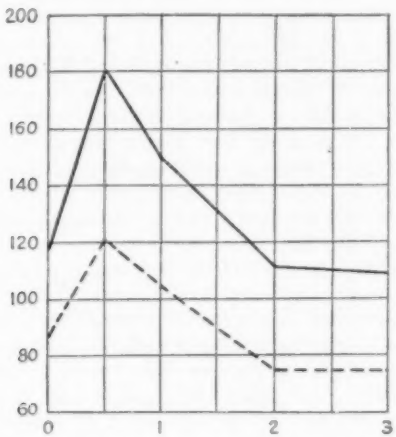
strated varying incidence of hepatic dysfunction in patients with Graves' disease. In those tests involving the metabolism of carbohydrates (glucose and galactose tolerance tests) [25, 26, 28] the authors pointed out that the abnormal results may be a reflection of multiple derangements of carbohydrate absorption and metabolism in thyrotoxicosis of which impaired hepatic handling is only a part. Therefore these tests may not be a true indication of the severity of hepatic involvement per se.

In addition to these clinical studies there have been parallel investigations of autopsy material in large series of patients who died with Graves' disease, excluding those with known independent hepatic disease.[5, 15, 17, 20, 41-48] With but one exception,[43] these authors have all described a variety of acute and chronic changes, occurring with remarkable consistency, over and beyond the changes of chronic passive congestion secondary to thyrotoxic heart disease. According to



GRAPH 1. Glucose tolerance tests (100 gm. glucose).

Beaver and Pemberton [5] the more acute lesions (fatty changes, central and focal necrosis) have been directly proportional to the severity of the thyrotoxicosis as measured by the basal metabolic rate while the more chronic lesions (atrophy and cirrhosis) have been more related to the duration of the disease.

Duplicating all these clinical studies have been a great many experimental studies in a wide variety of animals, largely rats and dogs but also cats, rabbits, guinea pigs and dormice. Experimental hyperthyroidism has been induced by the feeding of desiccated thyroid gland. The results have been in line with the findings in clinical cases of thyrotoxicosis. Pathological evidence of liver damage was demonstrated [29, 49, 50]; function studies with the use of bromsulfalein retention [51, 52] and IV galactose tolerance tests [29] have shown impairment; marked glycogen depletion of the liver and impaired glycogenesis have been demonstrated [53-56]; and both relative and absolute hypertrophy of the liver and spleen

found after thyroid feeding.[57-60] The depletion of liver glycogen in the thyroid fed mouse was once proposed as a biological test for Graves' disease by Himmelberger[61] who found that blood or urine of thyrotoxic patients injected into mice caused a prompt depletion of liver glycogen. A few authors[62, 63] reported failure to find demonstrable liver damage in experimental animals after thyroid feeding.

Thus there is an impressive body of evidence from functional study, clinical, pathological and experimental sources to establish the presence of impaired hepatic function as an integral part of the syndrome of thyrotoxicosis. Some authors have even drawn a parallel between so-called acute liver death and death in thyroid storm, and, on the basis of similarity in the clinical picture, sought to indict acute liver failure as the major causative factor in death by storm.[20, 64-68]

There is far less agreement, however, about *liver size* in Graves' disease. Experimental work in dogs and rats has indicated that a relative and even absolute hypertrophy of the liver occurs as the animal is made thyrotoxic and caused to lose weight.[57-60] On the other hand most human autopsy studies have shown a reduction in average weight, and simple atrophy has been a common anatomical finding.[5, 15, 17, 44, 69] However, several reports of clinical cases[6, 13, 14] definitely mention various degrees of hepatic enlargement, though most are silent on this point. Perhaps an explanation of the above findings can be effected by recalling the various anatomic changes in the liver seen at post mortem. Acute changes, especially those of fatty infiltration, can certainly cause enlargement of the liver and this would most likely be seen in the clinical cases; whereas the more chronic changes of atrophy and cirrhosis would lead to eventual shrinkage and this would be best seen in autopsy material.

Still less mention has been made of spleen size in the literature. The size of the spleen would be expected to increase with progressive liver involvement and probably continue to increase even when the cirrhotic liver decreases in weight. In two of the reports of experimental work with rats[57, 59] splenomegaly is mentioned; in three autopsy series of patients with Graves' disease the average size of the spleen was found to be normal in one,[69] slightly increased in another,[5] and definitely increased in the third.[44] Two case reports mention splenomegaly as part of the picture of acute hepatic dysfunction in thyrotoxicosis[13, 14] and Means[13] states in his textbook that "The spleen can be palpated in a few cases of toxic goiter."

Therefore, although liver damage in Graves' disease is well known and liver function studies have been incorporated into the preoperative work-up of thyrotoxic patients and been utilized as additional guides to management and to preparation for surgery, the fact that this liver damage can extend to palpable hepatosplenomegaly is far less known. It is thus felt to be of interest to report the following case of thyrotoxicosis with impaired hepatic function and with concomitant hepatosplenomegaly. This case is also of interest because it demonstrates again the reversibility of liver damage on this etiologic basis by proper therapy of the underlying thyrotoxicosis. This reversal of the liver damage is not to be universally expected as some of these patients go on to a progressive and permanent cirrhosis.[6, 23] But certainly the prognosis is much poorer if the relationship of the thyroid as the causative agent is not recognized and the thyrotoxicosis not adequately treated.

Case Report

A 19 year old male, in previous excellent health, was admitted on October 3, 1946 with a six to nine month history of nervousness, tremors, weakness, increased appetite, increased sweating, shortness of breath on exertion, evening ankle edema, and slight enlargement of the size of his neck. Initial physical examination revealed: a bilaterally palpable, slightly enlarged thyroid gland, without nodules; a warm moist skin, a slight stare, blood pressure of 145 mm. Hg systolic and 60 mm. diastolic, pulse rate of 108, an apical systolic murmur, a coarse tremor of the extended hands, and palpable liver and spleen each extending about two fingers' breadth below the costal margin. Impression on admission was thyrotoxicosis with hepatosplenomegaly, possibly due to liver damage secondary to Graves' disease.

Initial work-up included the following: basal metabolic rate (average of six calculations) +41; blood cholesterol (average of two) 119 mg. per cent; circulation time (average of two) 8.5 sec.;* normal blood counts except for a marked lympho-

Table I

Comparison of Tests of Thyroid and Hepatic Function

	On Admission	3 Mos. Postop.
1. Pulse pressure	85	40
2. Pulse rate	108	88
3. Circ. time (calcium gluconate)*	8.5 sec.	15 sec.
4. BMR*	+41	+3
5. Bl cholesterol	119	247
6. Lymphocyte percentage* in blood	67%	47%
7. Liver size	2 F B↘	2 F B↘
8. Spleen size	2 F B↘	barely palpable
9. BSP retention* (5 mg./kilo)	35%	7.5%
10. Oral hippuric test	1.39 G	2.9 G
11. Glucose tolerance curve (see graph)	abnormal	normal
12. Icterus index	7	9
13. Urine for bile and increased urobilinogen	negative	negative
14. Total protein	6.8	7.6
Albumin	5.3	4.4
Globulin	1.5	3.2
15. Prothrombin index	normal	normal

* Figures refer to average of several determinations.

cytosis of the peripheral blood of (average of three) 66 per cent. It was felt that the above findings of elevated basal metabolic rate, lowered blood cholesterol, decreased circulation time, and lymphocytosis of peripheral blood all fitted with and confirmed the clinical impression of thyrotoxicosis. Electrocardiogram was normal and chest roentgen-ray was normal with no evidence of substernal thyroid.

Because of the hepatosplenomegaly, the hepatic function was investigated. Bromsulfalein retention at 30 min. with 5 mg./kilo was 35 per cent; oral hippuric test revealed excretion of 1.39 gm. benzoic acid; glucose tolerance curve showed 118 mg. per cent fasting level; 180 at one-half hr.; 150 at one hour; 112 at two hours; 109 at three hours. Icterus index 7; total protein 6.8 gm. per cent with 5.3 gm. albumin and 1.5 gm. globulin. The urine was negative for bile and for increased urobilinogen; prothrombin index normal. Though some of these tests were normal, the more sensitive ones, bromsulfalein and oral hippuric, revealed a considerable degree of hepatic

* 3 c.c. calcium gluconate intravenously: arm to tongue time.

dysfunction and the glucose tolerance test showed a slight derangement of carbohydrate metabolism.

In an effort to rule out other possible causes of hepatosplenomegaly the following additional determinations were made: fragility of red cells, normal; malarial smears after adrenalin, negative; bleeding time two minutes, clotting time 1 min. 35 sec., reticulocyte count .1 per cent, platelet count 158,400. Hematocrit was 45 per cent, sedimentation rate 9 mm./hr. (Wintrobe method), urinalysis normal, Kahn negative.

After completion of these studies patient was prepared for surgery with Lugolization, high caloric diet, rest, sedation, and B vitamin supplements. The basal metabolic rate gradually fell to + 27 and after three weeks it was decided to operate. Immediately preoperatively bromsulfalein retention had fallen to 25 per cent in 30 min., and the oral hippuric test showed a rise in benzoic acid excretion to 2.55 gm.

Subtotal, one stage thyroidectomy was performed on December 17, 1946 under endotracheal gas-oxygen-ether anesthesia. Patient stood the procedure well and convalesced uneventfully. Pathological report on the excised thyroid gland revealed "small acini, lined by columnar epithelium, having no colloid. Some acini showed papillary infoldings and some larger acini contained eosin staining colloid. Definite increase in lymphocytic elements of the stroma and in some areas definite lymph follicles were noted. Diagnosis: Diffuse hyperplasia of thyroid with areas of regression."

Post-operatively basal metabolic rate determinations were + 1. and + 1. Bromsulfalein retention was 20 per cent at 30 minutes, oral hippuric test showed 2.08 gm. excretion, icterus index was 7, urine showed no bile and was positive for urobilinogen in 1:20 dilution. The liver and spleen were palpable as before. It was felt that the immediate postoperative period was too early to evaluate the possible effect of thyroidectomy on restoration of liver function and regression of liver and spleen size.

Patient was accordingly sent on a 60 day convalescent furlough and returned for reëvaluation on March 13, 1947. During the interval, patient had been in excellent health. Upon his return his blood pressure was 130 mm. Hg systolic and 90 mm. diastolic, his pulse 88, his spleen definitely smaller in size and now barely palpable, his liver apparently unchanged in size. Thyroid and liver function were both reëvaluated.

Basal metabolic rate was + 6, and 0; blood cholesterol 247; circulation time 15 sec., 15 sec.; white blood count 9,800 with 51 per cent polys and 47 per cent lymphocytes. The electrocardiogram and chest roentgen-ray were again normal as was hematocrit, white count, platelet count, sedimentation rate, urinalysis. Liver function studies revealed the following. Bromsulfalein (5 mg./kilo at 30 min.), 10 per cent and 5 per cent retention; oral hippuric excretion test 2.9 gm. benzoic acid; thymol turbidity 6 units (normal 0 to 10); ceph. floc. 1 + (unfortunately it had not been possible to obtain the last two mentioned tests preoperatively); glucose tolerance curve, 88 fasting level, 121 at one-half hour, 104 at one hour, 75 at two hours and 75 at three hours; total protein 7.6 gm. per cent with albumin 4.4 and globulin 3.2 gm.; prothrombin index normal, icterus index 9, urine negative for bile and for increased urobilinogen.

Thus three months postoperatively, not only had all clinical and chemical evidences of thyrotoxicosis reverted to normal but the spleen had definitely decreased in size and the results of all liver function tests revealed no significant abnormality.

Comment

Because of the rarity of reported hepatosplenomegaly as concomitants of thyrotoxicosis, numerous other diagnostic possibilities were explored in the work-up of this patient. The combination of hepatomegaly, splenomegaly and the marked lymphocytosis of the peripheral blood (64, 61, and 75 per cent) suggested the possibility of a somewhat atypical lymphatic leukemia with the associ-

ated elevated basal metabolic rate so often seen in leukemic patients. The absence of lymphadenopathy, of immature white cells in the peripheral blood and of anemia served to exclude this possibility. The reversal of the peripheral blood picture and of the splenomegaly after thyroidectomy was further evidence against the diagnosis of leukemia. The absence of increased red cell fragility, of spherocytes on blood smear, of signs of increased hemolysis, and of reticulocytosis served readily to differentiate familial hemolytic icterus. The patient had never been in a malarious area, had no history of fever and chills, and repeated smears after adrenalin were negative for malaria.

That the liver damage and hepatomegaly were not part of an independent cirrhosis of the liver was established by the reversal of the picture subsequent to thyroidectomy. There was incidentally no history of alcoholism or dietary deficiency of any type. The absence of icterus, of gastrointestinal symptoms, especially anorexia and nausea, and of the signs of acute illness ruled out a concomitant but unrelated acute infectious hepatitis. We were therefore left with the conclusion, amply supported by the evidence cited from the literature, that we were dealing with a case of liver damage secondary to thyrotoxicosis and that in this case the liver damage extended to the admittedly more rare presence of definite hepatosplenomegaly. This case is being reported largely to call attention to the fact that hepatosplenomegaly occurring in conjunction with Graves' disease can be part of the clinical picture and that it together with the chemical evidences of hepatic dysfunction can be expected to reverse itself when the underlying thyrotoxicosis is adequately treated.

The obvious corollary is that a careful evaluation of the hepatic function should be part of the work-up of every thyrotoxic patient, especially those in whom surgery is contemplated. The importance of this preoperative evaluation and the preoperative fortification of the damaged liver is stressed by numerous writers on this subject.[20, 21, 24, 66, 68, 70, 71] Of 250 patients with thyrotoxicosis seen in Schmidt's clinic, 60 per cent had a definite impairment of liver function on the basis of the oral hippuric acid test.[24] The magnitude of this relationship needs constant reëmphasis.

Summary

A case of relatively mild thyrotoxicosis with marked liver damage and secondary hepatosplenomegaly is presented. Attention is called to the fact that the liver damage so often found in patients with Graves' disease can be severe enough to cause definite enlargement of the liver and spleen and that these findings though unusual are not incompatible with the clinical picture of thyrotoxicosis. The hepatic dysfunction was reversed by subtotal thyroidectomy.

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GREAT REDUCTION IN HEART SIZE ATTENDING THE CLEARING OF CONGESTIVE HEART FAILURE IN A MAN WITH HYPERTENSIVE AND CORONARY HEART DISEASE *

By James H. Currens, M.D., and Paul D. White, M.D., F.A.C.P.,
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The treatment of many patients with cardiac dropsy has been discouraging in the past in spite of the use of digitalis and mercurial diuretics which oftentimes give striking temporary improvement. In the majority of patients with congestive failure resulting from hypertensive and coronary heart disease, however, experience has shown that edema and dyspnea return with monotonous regularity even though activities are kept at a minimum. In the past few years the importance of a low sodium dietary intake has become increasingly apparent as a means of preventing the re-appearance of all the signs of congestive heart failure, particularly among the patients with coronary and/or hypertensive heart disease.

We wish to present the following case report demonstrating what may be accomplished in certain patients who on initial examination show severe cardiac dropsy. This report demonstrates the reversibility of symptomatic heart disease

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in a patient with hypertensive and coronary heart disease by the use of all the measures which are available to the physician of today.

Case Report

A 61 year old physician was first seen in August, 1945, because of shortness of breath and dependent edema. The patient had always enjoyed good health, although he had been somewhat nervous all of his life. Seven years previously his blood pressure had been found to be elevated, the systolic level ranging from 180 to 200 millimeters of mercury. One year previously, in July, 1944, the patient was taken in the street with severe left anterior chest pain with radiation to the left arm. The pain lasted for 45 minutes, being relieved at that time by morphine. The following day, while he was at home in bed, the pain recurred and lasted one hour, again requiring morphine for relief. The patient was seen at this time by a competent cardiologist, and after reviewing the electrocardiograms he felt that the patient was suffering from coronary insufficiency but did not believe that a myocardial infarction had occurred. The patient was in bed four weeks and about the house for another month, after which time he returned to work.

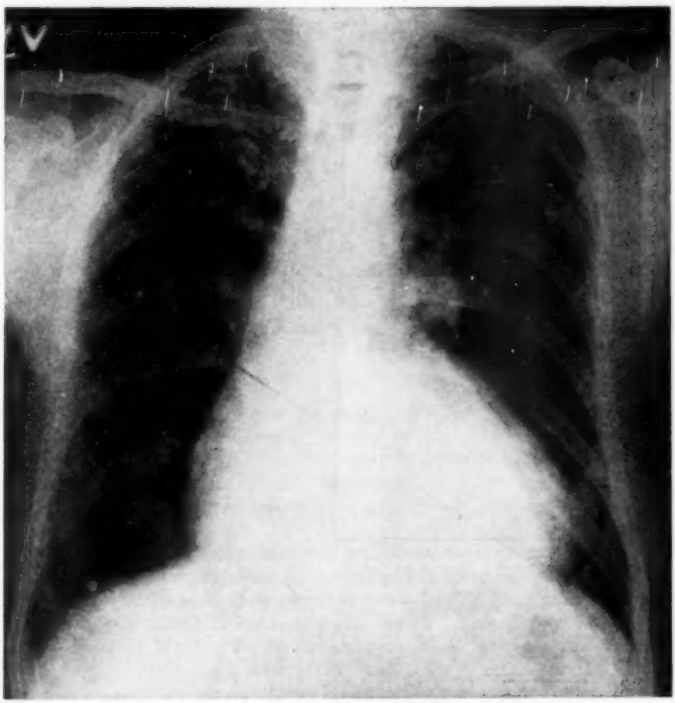

Fig. 1.

A. Teleroentgenogram of the chest on July 25, 1945, demonstrating a large heart measuring 19.6 centimeters in diameter.

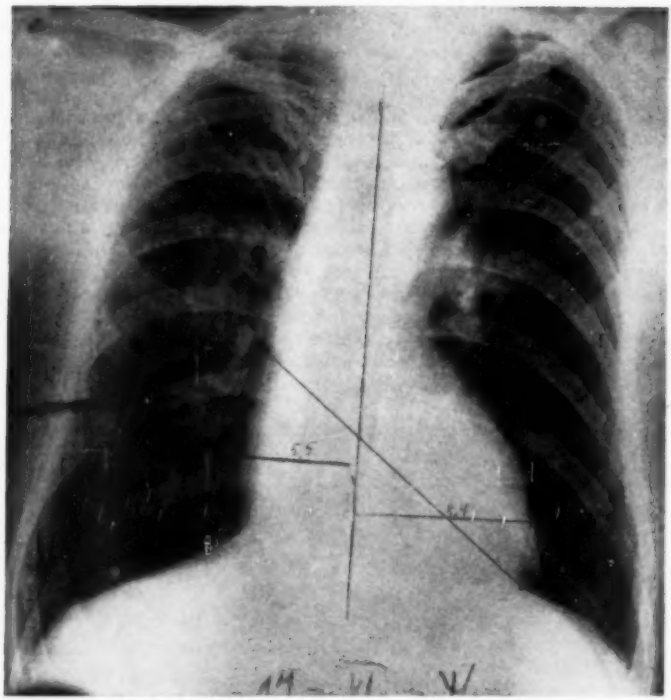

FIG. 1.

B. Repeat teleroentgenogram on June 12, 1946, shows a remarkable decrease in the size of the heart to 13.9 centimeters. The heart was found to be this same size in April, 1947.

Six months later, in February, 1946, the patient had an attack of paroxysmal nocturnal dyspnea, at which time he was placed upon digitalis and aminophyllin. He remained in bed at that time for one week. The following month he developed considerable dyspnea on effort and dependent edema in spite of his medication. His condition became gradually worse in spite of ammonium chloride and infrequent mercurial diuresis.

On physical examination the patient was found to have considerable orthopnea. The neck veins were distended and pulsating. A moderate number of moist râles were heard at each lung base. The heart was found to be considerably enlarged and the sounds were of poor quality. There was a loud apical protodiastolic gallop rhythm and the pulmonary second sound was accentuated. The blood pressure was 180 millimeters of mercury systolic and 116 millimeters diastolic, with a pulsus alternans of 2 to 4 millimeters of mercury. The liver was three to four fingers'-breadth below the right costal margin, and there was a high degree of edema of the sacrum and lower extremities. A chest film taken a few weeks before is illustrated in figure 1; the electrocardiograms at that time and subsequently are illustrated in figure 2.

The patient's revised treatment consisted of increasing the dosage of ammonium chloride from 3 grams to 6 grams per day and of digitalis to 0.2 gram each day for 10 days and mercurial diuresis (2 c.c. of Mercupurin) on three occasions. He was also placed upon a low sodium dietary regime. The diet contained about 0.5 gram of sodium per day with a neutral ash content. The fluids were increased from about 1400 c.c. a day to around 2000 c.c. a day. In the course of the next few weeks

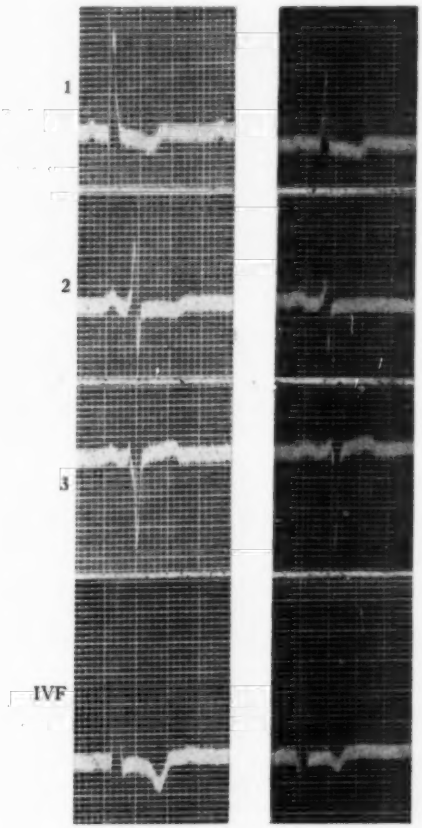

FIG. 2.

A. The electrocardiogram taken in July, 1944, several days after the patient had severe chest pain on two successive days. The pattern is quite characteristic of left ventricular strain and hypertrophy with or without the presence of coronary heart disease.

B. Repeat electrocardiogram of January, 1947, reveals little change, although the T waves in Leads I and IV are somewhat less negative and the R waves in Leads I and II shorter. There has been surprisingly little variation in the tracings from July, 1944, to January, 1947.

the patient lost 30 pounds in weight, the anasarca subsided, and the patient subjectively felt much improved.

The patient was last seen by us in April, 1947, almost two years after the first examination, at which time he was feeling well indeed, and he had had no recurrence of dyspnea or edema. He has continued with 0.1 gram of digitalis and 3 grams of ammonium chloride each day, and he has been very careful to avoid foods which contain any appreciable amounts of sodium. His food is cooked without salt, including his bread, but otherwise he eats a well-rounded diet. Fluids are taken as needed, which amounts to two to two and one-half liters each day.

Physical examination in April, 1947, revealed no evidence of venous pulsation in the neck, and no râles were heard in the chest. The heart was found to be on the borderline as to cardiac enlargement and the apex impulse was 8 centimeters to the left of the mid-sternal line in the fifth interspace. There were no murmurs or gallop rhythm. The blood pressure was 170 millimeters of mercury systolic and 104 to 110 millimeters diastolic. The liver was not palpable. No edema was discernible in the lower extremities. The blood and urine examinations showed no abnormalities. The non-protein nitrogen measured 25 milligrams per cent. A phenolsulphonephthalein urinary excretion test indicated 47 per cent excretion in two hours with 15 per cent excretion in the first 15 minutes. A roentgen-ray film demonstrated a striking reduction in the size of the cardiac silhouette in comparison with the chest film of July, 1945, and was similar to the film in figure 1B. The transverse diameter of the heart shadow had decreased by 5.7 centimeters.

He continues to do well, spending 12 hours a day in bed and doing not more than two hours of office work each day. A salt substitute containing equal parts of potassium chloride and potassium citrate has been used at times, but generally he does without this substitute. Although the food tastes quite flat, he seems to have adjusted himself well to the diet and does not feel the need for a salt substitute.

Discussion

The judicious increase in dosage of digitalis and ammonium chloride and in sodium restriction together with the use of mercurial salts parenterally resulted in a striking diuresis in this patient. In a relatively short period of time the dropsy disappeared and he was free of his bothersome orthopnea and dyspnea. During this time the amount of sodium lost in the urine must have been large, for we know that a person may lose 30 to 40 grams of sodium as sodium chloride following mercurial diuresis.

The use of the low-sodium diet was of the utmost importance from the long-range point of view since it helped prevent the re-accumulation of the dropsy. Without such a regimen it has been our experience in the past that the majority of these patients require periodic mercurial diuresis to maintain any reasonable health. By the use of mercurial diuretics one effectually increases the loss of water and sodium chloride. It is, however, more advantageous to limit the intake of sodium in order to prevent the accumulation of the dropsy as has been suggested repeatedly since 1941.[1-5]

The striking decrease in heart size is attributed to the decrease in blood volume time effected by the diuresis aided doubtless by adequate digitalization. The size of the heart has been found to reflect roughly the circulating blood volume. The reduction in size of this patient's heart has been greater than in most patients observed (except for a few myxedematous cases) in whom the reduction had been effected by sympathectomy or dietary treatment for hypertension or by subsidence of congestive heart failure with digitalization.

It is interesting to note that in spite of this remarkable reduction in heart size there was no commensurate improvement of the electrocardiogram, although there was a slight return toward the normal (figure 2). This is possibly accounted for by the presence of coronary heart disease with very likely some scarring of the myocardium. The continued hypertension may also be an important factor in the persistent electrocardiographic pattern. The change in the blood pressure was not remarkable in spite of the low sodium intake over a prolonged period of time. Other diets have been reported to be of value in the treatment of cardiac dropsy, the salient feature of which undoubtedly is the low sodium content.[4, 6, 7] An additional item of some importance in the course of this man's recovery may have been a subsidence of activity of coronary heart disease through the spontaneous development of collateral circulation which is of such common occurrence in the evolution of disease of the coronary arteries.

Summary

Remarkable decrease in heart size is reported in the case of a man aged 61 years treated for severe congestive heart failure secondary to hypertension and coronary arterial disease. The therapy included adequate digitalization, the use of ammonium chloride and mercurial diuretic, and a sharp restriction of sodium intake. The sodium restriction was in large measure doubtless responsible for the two years of good health that followed.

We wish to acknowledge the coöperation of Dr. Roberto Zachrisson, Guatemala City in the case of this patient.

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MYOCARDIAL INFARCTION RESULTING IN INTERVENTRICULAR SEPTAL PERFORATION; REPORT OF A CASE DIAGNOSED DURING LIFE *

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THIS report concerns a case of coronary thrombosis with infarction of the interventricular septum, in which perforation of the septum was diagnosed during life. Sager,[1] in 1934, gathered from the literature only 18 recorded cases (including one of his own) of perforation of the infarcted interventricular septum, the first of which was reported by Latham in 1845.[2] Wood and Livezey [4] found reference to 36 cases up to 1942. In a series of 25,000 consecutive autopsies, Edmondson and Hoxie [3] found 72 cases of cardiac rupture, among them 13 cases of septal perforation due to infarction. Additional cases have been reported by Moolton, Lober and Herzog, Wood, Weber, Bayley and Fader, Scott and Garvin, Master and Russell, Gross and Schwartz, and Stanley.

CASE REPORT

The patient, a woman aged 72 years, was admitted to Presbyterian Hospital, Chicago, on October 3, 1946, complaining of severe substernal pain with radiation down both arms into the forearms.

The patient had been aware of the existence of hypertension for a number of years (1934: blood pressure 160/95; 1940: 190/110; 1942: 155/90). She had been in good health until three days prior to admission, when, while shopping, she suffered severe "knot-like" substernal pain and a severe pain in the right shoulder and back accompanied by faintness and slight nausea. She returned to her hotel where she rested until the following evening, when, feeling quite well, she attended a theater, after which severe substernal pain recurred with radiation into both forearms. The patient was seen that evening by a physician who prescribed a hypodermic injection after which the patient felt better. The following morning she was awakened by a recurrence of pain with the previous radiation, called a doctor, and was hospitalized within a short time.

Physical examination revealed an elderly, moderately obese woman complaining of substernal pain and appearing pale and fatigued. Temperature on admission was 99.2 degrees; pulse rate 88 per minute; respirations 18 per minute; blood pressure 138/90. The pupils were moderately contracted (morphine) but reacted to light. Lungs were clear. Heart tones were noted to be distant, and no murmurs were audible. The rhythm was regular and no enlargement was noted on percussion of the cardiac borders. The liver was not palpable. There was no peripheral edema. Sedimentation rate (corrected) was 49 mm. per hour; white blood count 15,000 per cu. mm. The electrocardiogram was interpreted as indicating left axis deviation, anterior myocardial infarction, probably recent. Septal involvement was suggested on the basis of widening of QRS complexes (figure 1a).

The patient was free of additional symptoms from October 4, 1946, until the evening of October 7, when slight nausea was noted. The blood pressure had fallen to 118/70, the pulse rate had risen to 96 per minute, and the patient continued to show an elevation of temperature between 99.4 and 100.2 degrees. An electrocardiogram

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From the Medical Clinic, Presbyterian Hospital, Chicago, Illinois.

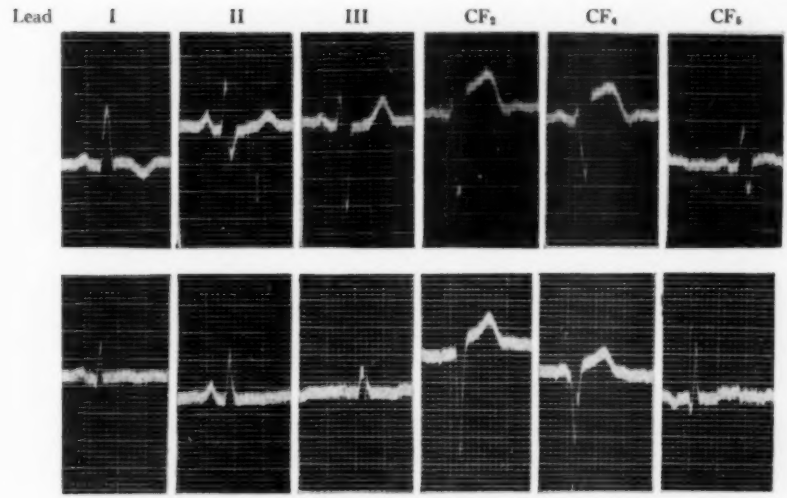

FIG. 1 A. (*above*) October 4, 1946. Day following admission to hospital.
FIG. 1 B. (*below*) October 7, 1946. Three days after admission to hospital.

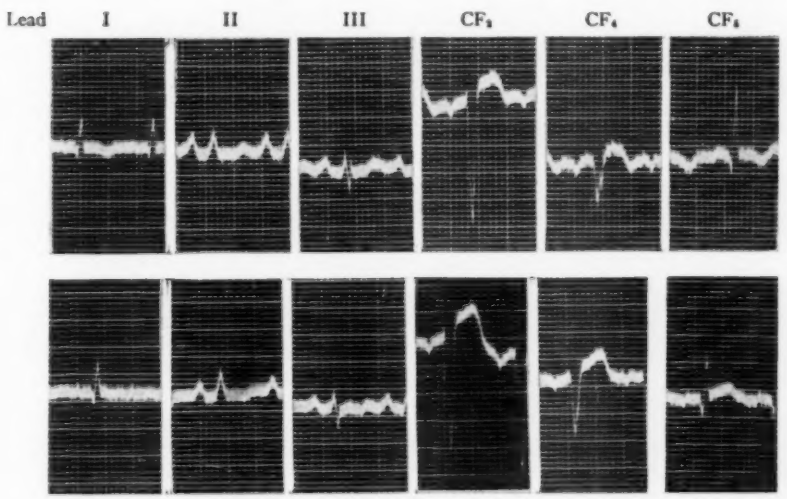

FIG. 1 C. (*above*) October 14, 1946. Ten days after admission, and six hours after septal perforation.
FIG. 1 D. (*below*) October 16, 1946. Twelve days after admission; two days after septal perforation, and four days prior to death.

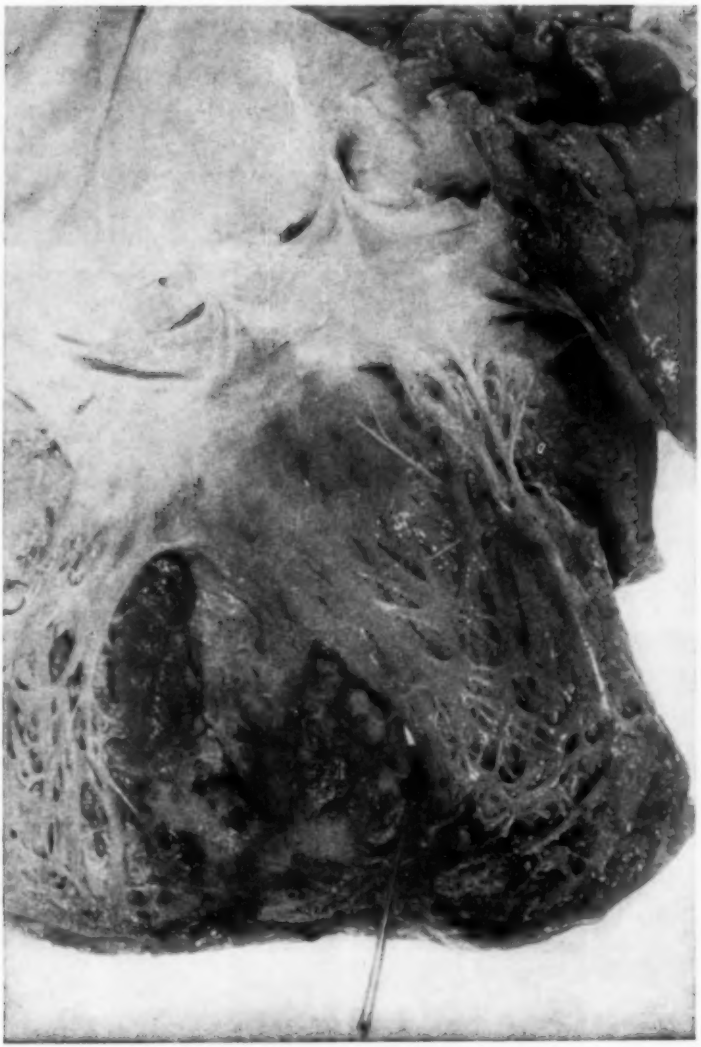

FIG. 2. View of the opened left ventricle showing the mural thrombus, the cut surface of the infarcted apex and probe lying in the septal perforation.

at this time indicated recent anterior myocardial infarction with suggested improvement in conduction in the precordial leads (figure 1b).

On October 9, five days after admission, and eight days following the onset of symptoms, crepitant râles were noted in the right lower lung field posteriorly, and

the patient developed slight dyspnea and non-productive cough. Heart tones were distant; no murmurs were audible. The patient was considered to have developed pulmonary edema incident to left ventricular failure due to recent severe myocardial infarction. Morphine and oxygen were effective in relieving the respiratory distress.

At 7:30 a.m. on October 14, the patient complained of nausea and pain in a rather localized area on the lateral surface of the middle one-third of the left arm.

FIG. 3. Right ventricular view of the septal perforation.

Examination revealed a pulse rate of 126 per minute, fine crepitant râles in both lung bases, and no heart murmurs. Three hours later, on examination by one of us (E. E. I.), the following note was made: ". . . at this examination the heart is rapid —about 112 per minute. Over the lower sternum there is a loud systolic murmur with occasional premature contractions. With each premature beat a shorter systolic murmur of same timbre as that of the regular beats is heard. Not a friction. Lungs . . . a few râles in left lower lateral chest. The right border seems by percussion as previously. Color of lips about same as yesterday (i.e. no cyanosis). No complaint of increased dyspnea. The probability of septal perforation must be considered." The murmur had never before been present, and was so loud that the possibility of its previously having been overlooked was considered untenable. A diagnosis of interventricular septal perforation due to infarction was made on the basis of the sudden appearance of a loud systolic murmur over the lower sternal region in a patient known to have had a recent severe myocardial infarction. No thrill was palpable. An electrocardiogram at this time indicated sinus tachycardia and recent myocardial infarction (figure 1c and d).

The condition of the patient became steadily worse during the following five days, with persistent nausea, marked weakness, and daily increasing evidence of left ventricular failure, as indicated by falling blood pressure, increasing pulmonary edema, rapid weak pulse, and weakening heart tones. Death occurred on October 20, the systolic murmur remaining audible almost to the time of death.

Pathologic Report (Dr. George Penick). The heart and aortic arch together weighed 425 gm. The epicardial surface was smooth. The left ventricular wall at the apex was infarcted, as evidenced by soft consistency and greenish-purple discoloration. In the left ventricle there was a mural thrombus measuring from 15 to 30 mm. in thickness, which was adherent to the endocardium of the left lateral wall of the ventricle and the left surface of the interventricular septum (figure 1). At the apex of the septum just anterior to the margin of the thrombus was a perforation which was edged with ragged, necrotic myocardium and which had a maximum diameter of 12 mm. (figures 2 and 3).

The coronary arteries were markedly sclerosed. The circumflex branch of the left artery was tortuous and its intima presented numerous calcified plaques. In spite of these plaques, its lumen averaged about 2 mm. in diameter. Extensive atherosclerosis had narrowed the lumen of the right coronary artery to an average diameter of less than 1 mm. A thrombus occluded the lumen of the anterior descending branch of the left artery at a point 2 cm. from the origin of this branch. Distal to the thrombus, the lumen was filled with coagulated blood for a distance of 2.5 cm. The extent of the infarction was determined by sectioning the formalin-fixed heart. Necrotic myocardium occupied an area 5 cm. square in the apical portion of the anterior wall of the left ventricle. The infarct extended into the inferior 3 cm. of the interventricular septum. Microscopic examination of sections from the area of infarction disclosed degenerating myocardial fibers with extensive intramuscular hemorrhage and a minimal leukocytic reaction, which were superimposed on a healing acute infarct, as evidenced by fibroblastic proliferation in adjacent regions.

Other cardiac findings were an anatomical patency of the foramen ovale and a lipoidal deposition in the cusps of the aortic and mitral valves.

Evidence of myocardial failure was found in an extensive pulmonary edema (overshadowed in the right lower lobe by an acute lobar pneumonia), and in an acute central necrosis of the hepatic lobules, accompanied by sinusoidal congestion and mild, parenchymal, fatty degeneration.

Peripheral embolism, presumably from the mural thrombus, had resulted in three subcapsular acute splenic infarcts. The brain was fixed in formalin and serially sectioned, but no emboli or other lesions were demonstrated.

Generalized, severe, intimal hyalinization was found in the arterioles throughout the viscera. In the kidneys this was accompanied by arterial and arteriolar nephrosclerosis as manifested by a firmly adherent renal capsule, cortical scarring, glomerular hyalinization, and tubular atrophy. Atrophy of a portion of the left renal cortex had resulted from compression by a cyst found in the capsule of this kidney. This cyst measured 5 cm. in diameter and was filled with uncoagulated, semi-solid, dark brown blood.

The other findings are listed below, together with those mentioned in the foregoing paragraphs, and were non-contributory to the clinical course of the patient.

The complete pathologic diagnoses in this case were:

Arteriosclerosis, generalized, severe, with calcification and ulceration. Thrombus, occlusive, in left coronary artery, anterior descending branch, 2 cm. distal to bifurcation. Infarct, acute, of myocardium of left ventricle, anterior wall, and of interventricular septum, apical. Perforation of interventricular septum, secondary to infarction. Thrombus, mural, left ventricular, of septal and lateral walls, adherent, organizing. Patency of foramen ovale, with apposition of primary and secondary septa. Atheromatosis of aortic and mitral valves, moderate. Edema, pulmonary, acute, bilateral, severe. Pneumonia, lobar, acute, right lower lobe. Necrosis, central, acute, congestive, of liver, with mild fatty degeneration. Edema, subcutaneous, of dorsa of feet, mild. Arteriosclerosis, severe, of spleen, pancreas, kidneys, adrenals, thyroid. Nephrosclerosis, arterial and arteriolar, moderate, bilateral. Degeneration, hyalin, of collagen, of renal pyramids. Cyst of renal capsule, left, with hemosiderosis. Atrophy of kidney, left, local, compression. Edema of intima of descending aorta. Infarcts of spleen, anemic, acute, multiple, subcapsular, with associated venous thrombosis and arteritis, acute. Perisplenitis, acute, mild. Hyaline deposits in spleen, corpuscular. Infarct, pulmonary, healed, peripheral, right middle lobe, small. Emphysema, marginal, of left lung, mild. Anthracosis, pulmonary, bilateral, mild. Atrophy, senile, of uterus, Fallopian tubes and ovaries. Cysts, Nabothian, of endocervical canal. Fibrosis of appendix, obliterative. Adhesions, fibrous, peritoneal, between parietal peritoneum and ileum, splenic flexure of colon, sigmoid colon, and between spleen and descending colon. Adhesions, fibrous, pleural, anterior, apical, of left lung. Hydrothorax, left, moderate (250 c.c.). Lipoma, subcutaneous, of left antecubital fossa.

Comment

The diagnosis of this condition should not be difficult if the possibility is kept in mind, in a patient with a known coronary thrombosis and myocardial infarction, the sudden development of a systolic murmur located over or slightly to the left of the lower portion of the sternum at the fourth and fifth intercostal space is highly suggestive of septal perforation. Myocardial infarction with rupture of a papillary muscle might conceivably cause confusion, although in this the murmurs are reported as more bizarre, less well localized and may be associated with considerable cardiac enlargement.[1] Left ventricular dilatation with systolic murmur is likely to develop more slowly.

The general appearance and condition of the patient were the same as ordinarily seen in infarction without perforation, and death occurred from the severity of the infarction rather than from the fact that the septum incidentally perforated in the process. The average length of life in 10 patients following septal perforation is reported to be between nine hours and seven days, with an average of 2.25 days (Edmondson and Hoxie[3]), although Wood and Livezey[4] report a case of a man 44 years of age who survived five years following septal perforation, ultimately dying in congestive failure.

Summary

A case of perforation of the infarcted interventricular septum is reported. It is suggested that the diagnosis of such a condition is not difficult if the possibility is kept in mind.

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EDITORIAL

SOME ASPECTS OF ADRENAL CORTICAL FUNCTION AND PITUITARY-ADRENAL RELATIONSHIPS

In April, 1949 Hench et al.[1] reported that the administration of one of the adrenal cortical hormones, 17-hydroxy-11-dehydrocorticosterone (Compound E), produced beneficial effects of a striking nature in a group of patients with advanced rheumatoid arthritis. Withdrawal of the hormone was followed by the recurrence of signs and symptoms of the disease. Essentially similar results were obtained in several patients who were given adrenocorticotropic hormone (ACTH) derived from hog pituitary. In a subsequent paper [2] these investigators reported that the administration of compound E to three patients with acute rheumatic fever was also followed by rapid subsidence of clinical evidences of the disease. These findings have recently been confirmed by Thorn et al.[3] who have, in addition, reported preliminary observations indicating a beneficial response in several patients with acute disseminated lupus erythematosus and gouty arthritis. Unpublished observations indicate that similar responses have occurred in several disease entities of allergic etiology.

In all these reports, the fact has been stressed that the observations were to be considered as of a preliminary nature. The periods of study have been relatively short. The possible toxic effects of long term administration of these agents have yet to be evaluated. Furthermore, the scarcity and expense of the hormones have precluded widespread and prolonged use. Nevertheless, these reports have not only aroused great interest but have resulted in considerable speculation regarding the mode of action of the agents. They have succeeded also in challenging certain time-honored, even though inadequate, concepts of the pathogenesis of these diseases. Although it is impossible at this time to provide a complete pharmacologic rationale for the action of these hormones, it may, nevertheless, be profitable to examine some of the known metabolic effects of the adrenal cortical steroid hormones as well as some aspects of the pituitary-adrenal relationship.

In a recent report Gaunt and Eversole [4] have provided a brief, but excellent perspective of the entire adrenal cortical problem. Stewart [5] stated

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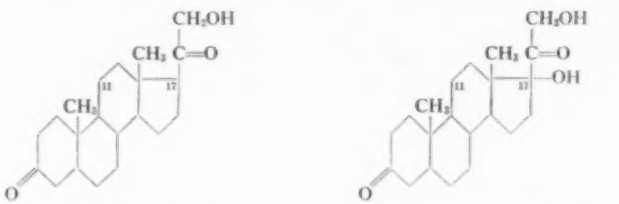
[4] Gaunt, R., and Eversole, W. J.: Notes on the history of the adrenal cortical problem, Ann. N. Y. Acad. Sci., 1949, l, 511.

[5] Stewart, G. N.: Adrenalectomy and the relation of the adrenal body to metabolism, Physiol. Rev., 1924, iv, 163.

in 1924 that although the available evidence indicated that the adrenal cortex was essential to life, knowledge as to how it functioned was quite unknown. The information was fragmentary and did not lend itself to unification. As late as 1930 Britton [6] stated that the meagerness of knowledge regarding cortico-adrenal function still did not permit rational theorizing. The modern history of adrenal cortex function may be said to have started in 1930 for it was in that year that Swingle and Pfiffner [7] were able to prepare the first good adrenal cortical extract. The first clinical trial of this material in Addison's disease occurred in the same year. It was assumed, at first, that only one cortical hormone existed. By 1936 various workers had demonstrated that a large number of steroid hormones could be crystallized from the adrenal cortex. In all, some 28 steroid hormones have been isolated from cortical extracts.[8] Six of these (vide infra) have been found to be capable of maintaining life in the adrenalectomized animal. Most investigators report the existence of an amorphous fraction which remains in their extracts after known steroids have been removed and which is highly active in maintaining life, but whose metabolic activities are but little understood. The only adrenal steroid for which a satisfactory and cheap method of synthesis became available early was desoxycorticosterone, customarily used as its acetate (DCA). This hormone was found to exert a profound effect on inorganic metabolism and to be quite potent in maintaining the life of patients with Addison's disease. Yet it is found only in very small quantities in the adrenal cortex. Great difficulties were encountered until recently in finding methods for the synthetic production of other adrenal steroids. The recent discovery by Kendall of an effective, if not cheap, method of partial synthesis is an important event in adrenal history.[9]



11-desoxycorticosterone

11-desoxy-17-hydroxycorticosterone (Compound S)

FIG. 1

The corticosteroids which lack oxygen at Carbon-11. The major effect of these compounds is upon inorganic metabolism.

[6] BRITTON, S. W.: Adrenal insufficiency and related considerations, Physiol. Rev., 1930, x, 617.

[7] SWINGLE, W. W., and PFIFFNER, J. J.: An aqueous extract of the suprarenal cortex which maintains the life of bilaterally adrenalectomized cats, Science, 1930, lxxi, 321.

[8] REICHSTEIN, T., and SHOPPEE, C. W.: The hormones of the adrenal cortex—in vitamins and hormones, Academic Press, Inc., New York, Vol. 1, p. 345.

[9] KENDALL, E. C.: The chemistry and partial synthesis of adrenal steroids, Ann. N. Y. Acad. Sci., 1949, 1, 540.

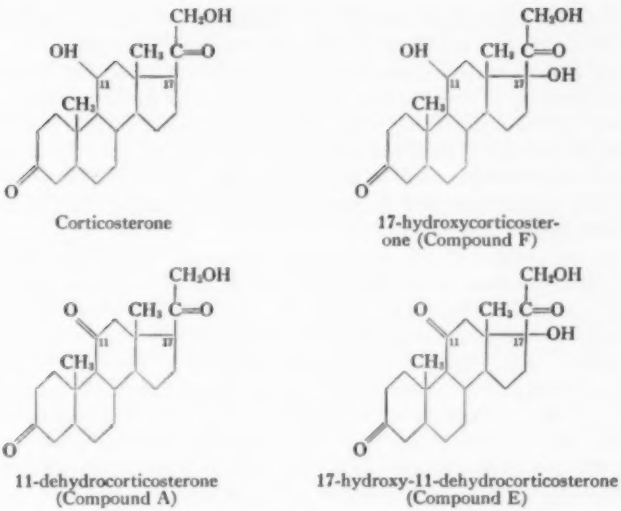


FIG. 2

The corticosteroids oxygenated at Carbon 11. These have a predominant effect on organic metabolism.

It is now known that the adrenal cortical steroids fall into three groups with reference to their physiological activity, namely, those which have a predominant effect on electrolyte and fluid balance, those which are concerned primarily with the intermediary metabolism of protein and carbohydrate, and those which have an androgenic and anabolic effect.[10] Any attempt to provide a concise summary of the rôle played by these steroids in physiological processes involves a great risk of oversimplification. Furthermore, it should be pointed out that there is experimental evidence of overlapping of functions between these groups. The lack of exact knowledge of the metabolic functions of the amorphous fraction leaves an unavoidable gap in any presentation of the subject at this time. With these limitations in mind a brief summary of the available information can be attempted.

For greater clarity of understanding the structural formulae of the six steroids which possess biological activity are presented (figures 1 and 2). It will be observed that the major difference between the two groups consists in the absence of an oxygen molecule (desoxy-) at Carbon 11 in the first group and its presence, in either keto- or hydroxy form, at Carbon 11 in the second group. The first group are known collectively, as desoxycorticosterones, while the latter are referred to as corticosterones. The adrenal

[10] SWINGLE, W. W., and REMINGTON, J. W.: The rôle of the adrenal cortex in physiological processes, Physiol. Rev., 1944, xxiv, 89.

steroids with androgenic activity are related in structure to testosterone but carry an oxygen molecule in position eleven (androsterone).

The desoxycorticosterones exert a regulatory effect on electrolyte and fluid balance by (1) acting directly upon the renal tubules, allowing them to conserve sodium and water and release potassium; (2) in a not-too-clear manner, determining fluid and electrolyte partitioning across cell membranes, capillary endothelium, and intestinal mucosa; (3) influencing sodium and potassium metabolism and thereby producing secondary effects upon extra- and intracellular hydration.

The oxygenated C–11 steroids are concerned primarily with the intermediary metabolism of protein and carbohydrate. Recent work has also demonstrated that these steroids exert a very definite effect upon the hematopoietic system, the details of which are considered below. Carbohydrate metabolism is influenced in the following general ways: (a) the corticosterones increase the conversion of fed carbohydrate to glycogen; (b) they influence the conversion of endogenous protein to glycogen (gluconeogenesis) by assisting either in the process of deaminization of amino acids or in the conversion of keto- and hydroxy acids to carbohydrate; (c) they diminish the oxidation of available carbohydrate.

Despite the enormous amount of work which has been done during the past several years, the details of the reactions into which the cortical hormones enter to bring about these metabolic effects are quite unknown. One must not confuse end results, such as those mentioned above, with the processes of action. In general, adrenal cortical deficiency leads to a disturbance in energy metabolism characterized by general "asthenia" of all the tissues, organs and organ systems which is reflected in a failure of the work capacity of the skeletal muscles, disturbance in certain renal functions, failure of lactation, decreased ability of the vasculature to withstand even minor stresses, and increased sensitivity of the organism as a whole to certain drugs and toxins. Recent work strongly suggests that hyperadrenocorticism manifests itself in a manner resembling Cushing's syndrome.[11]

It has become increasingly evident that the major regulatory factor of adrenal cortical function is the anterior pituitary. This regulation is achieved through the secretion of adrenocorticotropic hormone (ACTH). Long [12] states that as far as can be determined, all circumstances which enhance the secretion of the adrenal cortex can only do so by first activating the anterior lobe of the pituitary in consequence of which the required quantity of ACTH is released. It has long been known that hypophysectomy is followed by atrophy of the adrenal cortex, but not of the medulla. This atrophy can be prevented or the involuted glands restored to a normal condition by the administration of anterior lobe extracts. In 1933 Collip [13] reported the iso-

[11] Kepler, E. J.: Cushing's disease: a primary disorder of the adrenal cortices?, Ann. N. Y. Acad. Sci., 1949, l, 657.

[12] Long, C. N. H.: Conditions associated with secretion of adrenal cortex, Federation Proc., 1947, vi, 461.

[13] Collip, J. B., Anderson, E. M., and Thomson, D. L.: The adrenotropic hormone of the anterior pituitary lobe, Lancet, 1933, ii, 347.

lation, in impure form, of adrenocorticotropic hormone. However, it was not until 1943 that a pure form of the hormone, unadulterated by other secretions of the gland, was obtained by several groups of investigators.[14, 15] Since that time it has become possible, with greater precision, to study pituitary-adrenal relationships. In a manner common to other glandular interrelationships, there is apparently an internal self-regulatory mechanism between the adrenal cortex and the anterior pituitary. Increased concentration of corticosteroids in the circulating blood has an inhibitory effect upon the secretion of ACTH while a diminished quantity of the adrenal hormones results in antithetical activity.

The administration of ACTH is followed by striking morphological and biochemical changes in the adrenals of several animal species.[16] The biochemical changes largely concern the concentration of cholesterol and ascorbic acid. The adrenals contain a high concentration of cholesterol which is in a labile state. The administration of a single dose of ACTH results, within 3 hours, in a 50 per cent drop in the concentration of cholesterol in the gland. By the end of 24 hours the concentration of this substance has returned to normal. During the period of cholesterol depletion evidences of increased cortical hormone activity may be observed. Although no direct evidence exists as yet it is believed that the cholesterol is utilized in the formation of steroid hormones. Simultaneous depletion of the ascorbic acid content of the adrenal occurs after ACTH administration. This substance likewise reaccumulates to a normal concentration within 24 hours. The extremely sensitive response of adrenal ascorbic acid to ACTH is now utilized as a means of bioassay of ACTH potency. The exact relationship between ascorbic acid and the corticosteroids has not yet been established. The most striking morphologic change observed in the glands is hypertrophy. Sayers has stressed the fact that the reactions mentioned above must be looked upon as dynamic mechanisms which produce varying results depending upon the intensity and duration of the stimulus.

The significance of these observations is underscored by the fact that similar biochemical and morphological changes can be induced in the adrenals by a variety of situations which subject the animal to stress. Among the experimentally induced stress situations have been acute hemorrhage, exposure to extreme cold, scalding, stimulation of sensory nerves, operative procedures, injection of killed *B. coli*, and simulated altitudes of 20,000 feet. A variety of drugs, including histamine, epinephrine, ether, chloroform, etc., can also produce these effects. Similar treatment of previously hypophysectomized rats fails to produce a reduction of the cholesterol and ascorbic acid content of the adrenals. Long [12] believes that the common denominator

[14] Li, C. H., Evans, H. M., and Simpson, M. E.: The adrenocorticotropic hormone, Jr. Biol. Chem., 1943, cxlix, 413.

[15] Sayers, G., White, A., and Long, C. N. H.: Preparation and properties of pituitary adrenotropic hormone, Jr. Biol. Chem., 1943, cxlix, 425.

[16] Sayers, G., and Sayers, M. A.: The pituitary-adrenal system, Ann. N. Y. Acad. Sci., 1949, lv, 522.

which occurs in all of these situations is an excitation of the autonomic nervous system with the release of its specific hormone, epinephrine. Epinephrine injected subcutaneously, intravenously or intramuscularly can produce cholesterol and ascorbic acid depletion of the adrenals. This effect is abolished in the hypophysectomized rat. Furthermore, the previous administration of cortical hormones to the rat inhibits the reduction in adrenal cholesterol and ascorbic acid content presumably as a result of diminished ACTH production.

Several groups of investigators [17, 18, 19] have recently studied the effect of ACTH administration in man. Some studies were made after administration of a single dose of 25 mg. while others were done during a control period of 4–6 days during which the subjects received 40 mg. per day in divided doses. The results observed in normal individuals fall into several categories. There are a number of characteristic hematologic changes which include an average drop in the total eosinophile count of 75 per cent, an average drop of 45 per cent in lymphocytes, and an average increase in neutrophiles of 98 per cent. The metabolic changes observed included increased urinary excretion of uric acid, 17-ketosteroids, and potassium. Slight increase in fasting blood sugar levels occurred as well as slight increase in liver glycogen as determined by biopsy. There was also slight increase in body weight and striking decrease in the excretion of sodium. There was no significant elevation in either the diastolic or systolic blood pressures. No increase in the globulin content of the serum occurred nor was there any measurable antibody increase. These changes, in the aggregate, suggested that there had been stimulation of secretion of all the cortical steroids. In patients with Addison's disease these effects could not be produced after the administration of ACTH. Similar effects could, however, be produced in Addisonians by the injection of compound F. Desoxycorticosterone administered to Addisonians failed to produce the characteristic hematologic changes. It appears that these are mediated through the corticosterones.

A recent report by Hume presents evidence that the anterior hypothalamus constitutes an important link in the reaction of the body to stress. By producing localized lesions in a specific area of the hypothalamus, the formation of ACTH could be inhibited after stimuli which were ordinarily adequate for this purpose.

In the alarm reaction of Selye,[21] induced by a large variety of stress sit-

[17] Forsham, P. H., Thorn, G. W., Prunty, F. T. G., and Hills, A. G.: Clinical studies with pituitary adrenocorticotropin, Jr. Clin. Endocrin., 1948, viii, 15.

[18] Mason, H. L., Power, M. H., Rynearson, E. H., Ciaramelli, L. C., Li, C. H., and Evans, H. M.: The results of administration of anterior pituitary adrenocorticotropic hormone to a normal human subject, Jr. Clin. Endocrin., 1949, viii, 1.

[19] Sayers, G., Burns, T. W., Tyler, F. H., Jager, B. V., Schwartz, T. B., Smith, E. L., Samuels, L. T., and Davenport, H. W.: Metabolic actions and fate of intravenously administered adrenocorticotropic hormone in man, Jr. Clin. Endocrin., 1949, ix, 593.

[20] Hume, D. M.: The rôle of the hypothalamus in the pituitary-adrenal cortical response to stress, Jr. Clin. Invest., 1949, xxviii, 790.

[21] Selye, H.: The general adaptation syndrome and the diseases of adaptation, Jr. Clin. Endocrin., 1946, vi, 117.

uations, active participation of the anterior pituitary and adrenal cortex occupies a position of central significance. Selye has pointed out that the alarm reaction, however, is only one aspect, i.e. the first stage, of a syndrome which he calls the general adaptation syndrome. The other phases are the stage of resistance and the stage of exhaustion. In a comprehensive review, this investigator discusses the possibility that a variety of diseases such as hypertension, nephrosclerosis, rheumatic fever, and rheumatoid arthritis, to mention but a few, may be "diseases of adaptation" resulting from excessive or abnormal adaptive efforts involving the pituitary-adrenal system. With the expectation of an increased availability of purified hormones in the not too distant future these important concepts should offer fruitful sources for further intensive experimental investigation.

M. S. S.

REVIEWS

Arthritis and Allied Conditions. 4th Ed. By the late BERNARD I. COMROE, M.D.; completely revised and rewritten by JOSEPH L. HOLLANDER, M.D., and collaborators. 1108 pages. 16 × 24 cm. 1949. Lea and Febiger, Philadelphia. Price, $16.00.

Since Dr. Comroe's untimely death, advances in the field of rheumatism have made a revision of his standard work on arthritis inevitable. This has been undertaken and effected by a team of 17 leading rheumatologists. It is a tribute to Dr. Comroe's original work that much of its character and content graces the present edition.

The type has been somewhat compressed and, despite the inclusion of much new material, the present volume is shorter than the last edition by 250 pages. New chapters have been added on Joint Physiology, Rehabilitation of the Arthritic Patient, the Collagen Diseases, Rarer Forms of Metabolic Arthritis, Pregnancy in Arthritis and Reiter's Syndrome; and many new sections, such as those on the Shoulder-Hand Syndrome, Psychogenic Rheumatism, Normal Aging of Joints and Osteoporosis, have been included.

The editors have retained and increased the number of "summaries in box form" which have proved so valuable to those who have limited reading time and who use this book mainly as a work of reference. Often these are not true summaries, in that there is more information contained in them than in the relevant body of the text. For example the paragraph dealing with vaccines in the treatment of rheumatoid arthritis contains but 30 words, while the "summary" of the subject boasts over 130. This seems to represent a strange inversion.

Though this is undoubtedly a good text it is not as good as it should be. The large number of misprints and the many unnecessary repetitions in the text suggest to the reader hasty proof-reading and indifferent editing. The virtue of multiple authority has also the disadvantage of admitting contradictions.

It shows commendable enterprise to include reference to the new hormonal theory and therapy of rheumatoid arthritis. But one gets a little tired of seeing every allusion to adrenal cortical insufficiency, ACTH and substance E, paraded in italics or heavy black type. It may well prove, with time, to be the most significant of arthritic topics, but at the moment it is still the newest; and news is never as bad or as good as it sounds when it is first heard. It is too early to wave this flag so vigorously from the high eminence of a standard textbook.

The book is excellently illustrated with 370 figures including 160 new ones; it contains a wealth of practical detail and a large and up to date bibliography. As well as covering the entire field of rheumatology, many clinical entities, which seem far removed from arthritis but which can simulate "rheumatism" (sarcoidosis, bone tumors, scleroderma, and others), are well and fully discussed. These and many other good features make this authoritative publication a most useful encyclopedia of the rheumatic diseases. All in all it should justify the editors' hope that it will prove of value and interest to a wide variety of physicians.

H. J. L. M.

Textbook of Medicine. 8th Ed. By various authors; edited by SIR JOHN CONYBEARE, K.B.E., M.C., D.M. Oxon., F.R.C.P. 1170 pages; 22.5 × 14.5 cm. Williams and Wilkins Co., Baltimore. 1946. Price, $8.00.

This "Textbook of Medicine" is compiled from the efforts of many contributors and is divided into 19 sections. The first section is entitled "Infectious Diseases"

but is incomplete since the following three sections on "Tuberculosis," "Venereal Disease" and "Tropical Diseases" should be included under this heading. It seems misleading to classify such diseases as bacillary dysentery, amebic dysentery, typhus fever, rabies, malaria, and "effects of heat" as tropical diseases. Certainly, they are all illnesses found in nontropical areas, and it is unfair to stress them as regional diseases, especially to students. The pneumonias are separately grouped under "Diseases of the Lungs."

There is a section on the Diseases of Infants. Rickets is discussed in this section. The other vitamin deficiency diseases are included under "Diseases of Metabolism." There is no mention of vitamin A deficiency.

The subject matter is often handled with such brevity as to render it useless to all intent and purpose. So far as the reviewer can determine, no mention is made of tularemia, torulosis, ornithosis, acute arteritis, toxoplasmosis, porphyria, Haverhill fever, and splenic neutropenia.

This textbook is not impressive in either its organization or content.

E. C.

An Atlas of Electrocardiography. By WILLIAM DRESSLER, M.D., Cardiologist, Maimonides Hospital, Brooklyn, Consultant in Cardiology, The Brooklyn Hospital, Lecturer in Medicine, Long Island College of Medicine; and HUGO ROESLER, M.D., F.A.C.P., Cardiologist, Department of Medicine, Associate Professor of Radiology, Temple University Medical School and Hospital. 503 pages, 27.5 × 21 cm. Charles C. Thomas, Springfield, Ill. 1949. Price, $14.00.

This atlas is intended for those already conversant with the fundamentals of electrocardiography. Section I deals with electrocardiographic patterns excluding rhythm disturbances. Section II is devoted to disturbances of rhythm. Section III is concerned with advances in the electrocardiographic diagnosis of myocardial infarction. Section IV is a short section on unipolar leads.

In the first two sections, tracings which display similar patterns are arranged together, and the differential diagnosis is discussed. A summary of the clinical data is presented in addition to the electrocardiographic comment. This arrangement is valuable for teaching purposes and is commended. The section on disturbances of heart rhythm is especially good.

Most of the precordial leads shown are CF or CR; there are comparatively few records with V leads. The discussion of inverted T waves in Lead III makes no mention of variation of T_3 with respiration, and no example of this common finding is shown. Statements are made concerning the localization of myocardial damage which are based upon the electrocardiograms shown, which in some instances are such that pathological confirmation would seem desirable. The records interpreted as indicating anterior myocardial infarction in the presence of left bundle branch block are very interesting, and would prove more valuable were postmortem studies available. The authors devote a good deal of space to records with the "T_1 smaller than T_3" pattern. They state that notching of T is probably equivalent to inversion of T. There are occasional references to certain electrocardiographic findings as reflecting "a positional peculiarity of the heart"; but more specific details of position or supporting information are not presented.

This text generally is interesting and informative, and possesses many virtues. These overshadow minor faults, which will probably disappear in future editions.

S. S.

Clinical Biochemistry. 4th Ed. By ABRAHAM CANTAROW, M.D., Professor of Biochemistry, Jefferson Medical College; and MAX TRUMPER, Ph.D., Commander, H(S), USNR., Lecturer in Clinical Biochemistry and Basic Science Coördinator, Naval Medical School, National Naval Medical Center, Bethesda, Md. 642 pages; 15.5 × 24 cm. W. B. Saunders Co., Philadelphia. 1949. Price, $8.00.

In this edition of "Clinical Biochemistry," as well as in the earlier editions, the authors have applied current biochemical knowledge to problems in the diagnosis and treatment of disease. The chapters which have been revised include: renal and respiratory regulation of acid-base balance; pigment metabolism in relation to jaundice; carbohydrate, lipid and protein metabolism; thyroid function; absorption and storage of iron; action of parathyroid hormone; renal physiology; vitamins; experimental diabetes. A number of new topics have also been added.

Although this edition should serve as a good reference volume, the apparent attempt to limit the size to that of the previous editions appears to have been a handicap in the discussion of some of the material while some topics of relatively little current interest are still included. The bibliography is extensive but includes relatively few references later than 1945.

M. A. A.

Cardiovascular Disease. By LOUIS H. SIGLER, M.D., F.A.C.P., Attending Cardiologist and Chief of Cardiac Clinic, Coney Island Hospital; Consulting Cardiologist, Rockaway Beach Hospital and Menorah Home and Hospital for the Aged. 551 pages, 15.5 × 23.5 cm. Grune & Stratton, New York. 1949. Price, $10.00.

This new book contains chapters on most topics usually covered in other textbooks on cardiovascular disease. Often explanations of cardiac mechanisms are incomplete or are abruptly terminated with such statements as "the mechanism (auricular flutter with varying block) is fully discussed elsewhere," or "the mechanism (interference dissociation) has been fully described elsewhere," or "the reasons for these differences are given elsewhere." In each instance "elsewhere" is a reference to the author's textbook of electrocardiography. The rôle of the electrocardiogram in the diagnosis of myocardial infarction is covered with the statement. "The most important single aid in the diagnosis of coronary occlusion is the electrocardiogram. A complete discussion of the electrocardiographic diagnosis of myocardial infarction is given elsewhere." As for angina pectoris, "Electrocardiographic findings, described elsewhere, may also help in arriving at a diagnosis." It is recommended that one try to discover the presence of a hyperactive carotid sinus reflex as "an important aid in the diagnosis of the anginal syndrome due to coronary sclerosis." "A person who develops coronary occlusion which results in no myocardial damage should be allowed out of bed after three or four days of careful follow-up and the demonstration of the absence of such damage." Details as to how a diagnosis of coronary occlusion with no myocardial damage may be established in that length of time are not presented.

Careful examination of this volume reveals no compelling reason why it should replace the standard texts on this subject.

S. S.

BOOKS RECEIVED

Books received during September are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later but it is not possible to discuss all of them.

Behandlung innerer Krankheiten: Richtlinien und Ratschläge für Studierende und Ärzte. By PROF. DR. FERDINAND HOFF. 471 pages; 24.5 × 17.5 cm. 1949. Georg Thieme Verlag, Stuttgart. Price, geb. DM 25.—

Bentley's Text-book of Pharmaceutics. 5th ed. Revised by HAROLD DAVIS, B.Sc., Ph.D. (Lond.), Ph.C., F.R.I.C., Pereira Medallist, Sometime Chief Pharmacist, University College Hospital, London, with the collaboration of M. W. PARTRIDGE, B.Pharm., B.Sc., Ph.D. (Lond.), Ph.C., Lecturer in Chemistry, University of Nottingham, and A. I. ROBINSON, Ph.C., Late Pharmacist in Charge, Manufacturing Laboratory, Messrs. Stafford Allen & Sons, Ltd., London, with contributions by W. A. BROOM, B.Sc. (Lond.), F.R.I.C., M. ELLIS, M.Sc. (Wales), F.L.S., and H. A. TURNER, B.Sc. (Lond.), Ph.C., D.B.A. (Pharm. Soc.), Pereira Medallist. 1100 pages; 22.5 × 14.5 cm. 1949. The Williams & Wilkins Company, Baltimore. Price, $7.50.

Clinical Biochemistry. 4th ed. By ABRAHAM CANTAROW, M.D., Professor of Biochemistry, Jefferson Medical College, etc., and MAX TRUMPER, Ph.D., Commander, H(S), USNR., Lecturer in Clinical Biochemistry and Basic Science Coordinator, Naval Medical School, National Naval Medical Center, Bethesda, Maryland. 642 pages; 24 × 15.5 cm. 1949. W. B. Saunders Company, Philadelphia. Price, $8.00.

Fundamentals of Otolaryngology: A Textbook of Ear, Nose and Throat Diseases. By LAWRENCE R. BOIES, M.D., Clinical Professor of Otolaryngology, Director of Division of Otolaryngology, University of Minnesota Medical School, and Associates: CHARLES E. CONNOR, M.D., ANDERSON C. HILDING, M.D., JEROME A. HILGER, M.D., JOHN J. HOCHFILZER, M.D., CONRAD J. HOLMBERG, M.D., KENNETH A. PHELPS, M.D., ROBERT E. PRIEST, M.D., and GEORGE M. TANGEN, M.D. 443 pages; 24 × 15.5 cm. 1949. W. B. Saunders Company, Philadelphia. Price, $6.50.

Gemeinsame Erkrankungen aus der inneren Medizin und Chirurgie. By WALTHER KANERT and KURT AUGUST KOELSCH. 500 pages; 24.5 × 17.5 cm. 1949. Georg Thieme Verlag, Stuttgart. Price, geb. DM 35.—

Hemorrhagic Disorders: A Guide to Diagnosis and Treatment. By PAUL M. AGGELER, M.D., Assistant Clinical Professor of Medicine, and S. P. LUCIA, M.D., Professor of Medicine, University of California Medical School. Lettered and illustrated by PHYLURIA GIBBS, HELENE CLEARE and JEAN THOMPSON, under the supervision of RALPH SWEET. 112 pages; 28 × 22 cm. 1949. The University of Chicago Press, Chicago. Price, $10.00.

Lehrbuch der inneren Medizin. By DR. ERNST LAUDA. 569 pages; 25 × 17.5 cm. 1949. Springer-Verlag, Vienna. Price, $7.20.

Medical Clinics on Bone Diseases: A Text and Atlas. 2nd ed. By I. SNAPPER, M.D., formerly Professor of Medicine, University of Amsterdam, The Netherlands, etc. 308 pages; 28.5 × 22 cm. 1949. Interscience Publishers, Inc., New York. Price, $20.00.

Medizin in Bewegung: Klinische Erkenntnisse und ärztliche Aufgabe. By RICHARD SIEBECK. 520 pages; 24.5 × 17 cm. 1949. Georg Thieme Verlag, Stuttgart. Price, geb. DM 27.—

Memories of Eighty Years. By JAMES B. HERRICK. 270 pages; 23 × 15.5 cm. 1949. The University of Chicago Press, Chicago. Price, $5.00.

Nervous and Neurohumoral Regulation of Intestinal Motility. By W. B. YOUMANS, Professor of Physiology, University of Oregon Medical School. 129 pages; 24 × 15.5 cm. 1949. Interscience Publishers, Inc., New York. Price, $4.75.

The 1949 Year Book of Medicine (July, 1948–May, 1949). Edited by PAUL B. BEESON, M.D., J. BURNS AMBERSON, M.D., GEORGE R. MINOT, M.D., S.D., F.R.C.P. (Edinburgh and London), WILLIAM B. CASTLE, M.D., S. M. (Hon.) Yale, M.D. (Hon.) Utrecht, TINSLEY R. HARRISON, M.D., and GEORGE B. EUSTERMAN, M.D. 831 pages; 18.5 × 12.5 cm. 1949. Year Book Publishers, Inc., Chicago. Price, $4.50.

Operations of General Surgery. 2nd ed. By THOMAS G. ORR, M.D., Professor of Surgery, University of Kansas School of Medicine. 890 pages; 27 × 19 cm. 1949. W. B. Saunders Company, Philadelphia. Price, $13.50.

Pharmaceutical Compounding and Dispensing. Editor-in-Chief: RUFUS A. LYMAN, M.D., Dean, College of Pharmacy, University of Arizona. Advisory Editors: JAMES M. DILLE, Ph.D., ANDREW G. DUMEZ, Ph.D., GLENN L. JENKINS, Ph.D., RUDOLPH A. KUEVER, Ph.C., HUGH C. MULDOON, D.Sc., and HOWARD C. NEWTON, Pharm.D. Technical Editor: GEORGE URDANG, Ph.G., D.Sc. Nat. 321 pages; 26 × 18 cm. 1949. J. B. Lippincott Company, Philadelphia. Price, $6.50.

Physiology in Diseases of the Heart and Lungs. By M. D. ALTSCHULE, Assistant Professor of Medicine, Harvard Medical School, etc. 368 pages; 21.5 × 14.5 cm. 1949. Harvard University Press, Cambridge. Price, $5.00.

Physiology in Health and Disease. 5th ed. By CARL J. WIGGERS, M.D., D.Sc., F.A.C.P., Professor of Physiology and Director of Physiology Department in the School of Medicine of Western Reserve University, Cleveland. 1242 pages; 24 × 15.5 cm. 1949. Lea & Febiger, Philadelphia. Price, $10.00.

Pollen-Slide Studies. By GRAFTON TYLER BROWN, M.D., F.A.C.P., Instructor in Clinical Medicine, Georgetown University School of Medicine, etc. With a Foreword by WALLACE M. YATER, M.D., M.S. (in Medicine), F.A.C.P., Director, Yater Clinic, etc. 122 pages; 23.5 × 15.5 cm. 1949. Charles C. Thomas, Publisher, Springfield, Illinois. Price, $6.00.

Principles of Human Physiology, Originally written by Prof. E. H. Starling, M.D., F.R.C.P., C.M.G., F.R.S. 10th ed. By C. LOVATT EVANS, D.Sc., F.R.C.P., F.R.S., LL.D. Birmingham, Jodrell Professor of Physiology in University College, London. The Chapters on the Special Senses by H. HARTRIDGE, M.A., M.D., ScD., F.R.S., Director of Vision Research Unit (Medical Research Council), Institute of Ophthalmology, London. 1193 pages; 25 × 16 cm. 1949. Lea & Febiger, Philadelphia. Price, $10.00.

Reports on Biological Standards. III. Methods of Biological Assay Depending on a Quantal Response. Medical Research Council Special Report Series No. 183. By J. H. GADDUM. 48 pages; 24.5 × 15 cm. (paper-bound). 1933; reissued May 31, 1949. His Majesty's Stationery Office, London. Price, one shilling net.

Stedman's Medical Dictionary. 17th revised ed. Edited by NORMAN BURKE TAYLOR, M.D., F.R.S.C., F.R.C.S. (Edin.), F.R.C.P. (Can.), M.R.C.S. (Lon.), University of Western Ontario, etc.; in collaboration with ALLEN ELLSWORTH TAYLOR, D.S.O., M.A. 1361 pages; 24 × 16 cm. 1949. The Williams and Wilkins Company, Baltimore. Price, $8.50 with thumb index; $8.00 without thumb index.

Streptomycin and Dihydrostreptomycin in Tuberculosis: Reports of Research Including Studies Sponsored by the American Trudeau Society (Medical Section, National Tuberculosis Association). Edited by H. McLEOD RIGGINS, M.D., and H. CORWIN HINSHAW, M.D. 554 pages; 23.5 × 16 cm. 1949. National Tuberculosis Association, New York. Price, $7.50.

Subalimentación crónica y Esprue. By DR. ARSACIO PEÑA YÁÑEZ. 189 pages; 25.5 × 18 cm. (paper-bound). 1949. Editorial Cientifico Medica, Barcelona, Spain.

A Synopsis of Medicine. 9th ed. By SIR HENRY LETHEBY TIDY, K.B.E., M.A., M.D., B.Ch. (Oxon.), F.R.C.P. (Lond.), Extra Physician to H.M. The King, etc. 1243 pages; 19 × 12.5 cm. 1949. The Williams & Wilkins Company, Baltimore. Price, $7.50.

A Text-book of Pharmacognosy. 5th ed. By GEORGE EDWARD TREASE, B.Pharm., Ph.C., F.R.I.C., F.L.S., Reader in Pharmacognosy and Head of the Department of Pharmacy in the University of Nottingham. Revised with the assistance of H. O. MEEK, Ph.C., H. E. STREET, B.Sc., Ph.D., Ph.C., and E. O'F. WALSH, B.Sc., Ph.D., A.R.I.C., Ph.C. 811 pages; 22.5 × 14.5 cm. 1949. The Williams and Wilkins Company, Baltimore. Price, $8.00.

Tom Cullen of Baltimore. By JUDITH ROBINSON. 435 pages; 23.5 × 16 cm. 1949. Oxford University Press, New York. Price, $3.50.

Von der Angst der Kranken. By PROF. DR. MED. KARL SCHEELE. 76 pages; 21 × 14.5 cm. (paper-bound). 1949. Georg Thieme Verlag, Stuttgart. Price, kart. DM 4.80.

A Year With Osler—1896–1897. Notes taken at his Clinics in The Johns Hopkins Hospital. By JOSEPH H. PRATT, a Member of the Class of 1898. 209 pages; 23.5 × 15.5 cm. 1949. The Johns Hopkins Press, Baltimore. Price, $4.00.

COLLEGE NEWS NOTES

The 1949 Directory of the College

The new and revised Directory of the American College of Physicians is expected off press, ready for mailing to all who placed orders, before the end of the year. The forms closed on October 1, 1949, and thus the Directory will not contain additions to its membership after that date. The price to members of the College is $4.00, postpaid; to non-members and institutions, $5.00. Those who have previously placed their orders will receive statements after delivery of the Directory.

Gift to the College Library

Dr. S. T. Laufer, F.A.C.P., Halifax, Nova Scotia, recently presented to the Library of the American College of Physicians a very old manuscript, entitled (as translated), "Clinical Medicine," which was written in longhand and in Latin at Naples, Italy, in 1709, by Nicholaus Corazzelli. It is an orderly book following amazingly closely current case reports and medical texts. It gives the title of the disease, its recognized symptoms and causes, the diagnosis, prognosis and treatment. It is interesting to find in a manuscript prepared so long ago so many diseases then recognized and named, the names persisting to the present time.

A.C.P. Postgraduate Courses

The following postgraduate courses offered by The American College of Physicians on its Autumn, 1949, schedule are the only ones remaining open for registration:

COURSE NO. 7—BLOOD DYSCRASIAS

(December 6–10, 1949)

Medical College of Alabama

Birmingham, Ala.

James B. McLester, M.D., F.A.C.P., *Director*

Fees: A.C.P. Members, $30.00
V. A. (P. L. 346), $30.00
Non-members, $60.00

Officers of Instruction

Medical College of Alabama

Roy R. Kracke, M.D., Dean and Professor of Clinical Medicine.
Roger D. Baker, M.D., Professor of Pathology.
Charles E. Butterworth, Jr., M.D., Resident in Hematology, Jefferson-Hillman Hospital.
Arthur Chenoweth, M.D., Assistant Professor of Surgery.
Joseph K. Cline, Ph.D., Professor of Cancer Research.
Walter B. Frommeyer, Jr., M.D., Instructor in Medicine (Hematology).
James B. McLester, M.D., F.A.C.P., Associate Professor of Medicine and Executive Officer of the Department.

WILLIAM H. RISER, JR., M.D., Associate Professor of Medicine.
G. HARMON STOKES, M.D., Former Resident in Hematology, Jefferson-Hillman Hospital.

Visiting Faculty

GOULD A. ANDREWS, M.D., Chief of Hematology, Medical Division, Oak Ridge Institute of Nuclear Studies, Oak Ridge, Tenn.
W. R. ARROWSMITH, M.D., Instructor in Medicine, Tulane University of Louisiana School of Medicine, New Orleans, La.
IVAN W. BROWN, JR., M.D., Instructor in Surgery, Duke University School of Medicine, Durham, N. C.
MARSHALL BRUCER, M.D., Oak Ridge Institute of Nuclear Studies, Oak Ridge, Tenn.
W. J. DARBY, M.D., Professor of Biochemistry and Assistant Professor of Medicine, Vanderbilt University School of Medicine, Nashville, Tenn.
L. W. DIGGS, M.D., Professor of Medicine, University of Tennessee College of Medicine, Memphis, Tenn.
CHARLES M. HUGULEY, JR., M.D., Instructor in Medicine, Emory University School of Medicine, Emory University, Ga.
EDGAR JONES, M.D., F.A.C.P., Associate Professor of Clinical Medicine, Vanderbilt University School of Medicine, Nashville, Tenn.
R. WAYNE RUNDLES, M.D., Associate in Medicine, Duke University School of Medicine, Durham, N. C.
HOWARD E. SKIPPER, Ph.D., Associate Director and Director of the Division of Biochemistry, Southern Research Institute, Birmingham, Ala.

This is a new course on the College schedule. It is especially scheduled to meet a demand to furnish advanced instruction in the field of Hematology to physicians in the Southeastern part of the country. Outstanding authorities are being invited from the University of Tennessee, Emory University, Vanderbilt University, Duke University, Tulane University of Louisiana and the Oak Ridge Institute of Nuclear Studies to join the faculty. Advanced instruction will be offered in the form of lectures, case reports and staff conferences in the mornings and laboratory studies in the afternoons.

The last day of the course, Saturday, December 10, will be devoted to the Southeastern Regional Meeting of The American College of Physicians comprising Alabama, Florida, Georgia, South Carolina and Cuba. Every registrant is urged to remain for the Regional Meeting. Dr. E. Dice Lineberry, F.A.C.P., Governor for Alabama, is the General Chairman and Dr. Edgar G. Givhan, Jr., F.A.C.P., is Chairman of the Committee on Arrangements. The Regional Meeting program will be printed as a separate folder and will be supplied in advance to everyone in the course.

Hotel Accommodations: Tutwiler Hotel. Rates: Single rooms, $3.50 to $6.50; double rooms, $5.50 to $8.50; twin-bedded rooms, $6.00 to $8.50. Make reservations through Dr. D. O. Wright, 2930 North 16th St., P. O. Box 2603, Birmingham, Ala.

OUTLINE OF COURSE

Tuesday, December 6

THE ANEMIAS

A.M. Session

8:30	Registration, Assembly and Announcements.
9:00– 9:30	Diagnosis and Treatment of Pernicious Anemia. DR. JONES.
9:30–10:00	Diagnosis and Treatment of Nutritional Anemias. DR. DARBY.

10:00–10:30 Problems of Iron Metabolism.
DR. ARROWSMITH.
10:30–11:00 Diagnosis and Treatment of Hemolytic Anemias.
DR. HUGULEY.
11:00–11:30 Sickle Cell Anemia.
DR. DIGGS.
11:30–12:00 Evaluation of Hematopoietic Agents.
DR. JONES.
12:00–12:30 Megaloblastic Anemias from Gastrointestinal Diseases.
DR. DARBY.
12:30– 1:00 Diagnosis and Treatment of Hypochromic Anemias.
DR. ARROWSMITH.

P.M. Session

2:00– 4:00 Laboratories on Sixth Floor of Jefferson Hospital for microscopic work, lantern slide demonstrations, and examination of patients by Officers of Instruction and Visiting Faculty.

Wednesday, December 7

THE LYMPHOMAS

A.M. Session

9:00– 9:30 A Fundamental Search for Antileukemic Agents.
DR. SKIPPER.
9:30–10:00 Treatment of Chronic Leukemia.
DR. RISER.
10:00–10:30 Use of Folic Acid Antagonists in the Treatment of Acute Leukemia.
DR. KRACKE.
10:30–11:00 Treatment of Multiple Myeloma.
DR. RUNDLES.
11:00–11:30 Use of Hematology in Radiophysiology.
DR. BRUCER.
11:30–12:00 Radio-active Isotopes in the Treatment of Leukemia.
DR. ANDREWS.
12:00–12:30 Metastatic Tumors in Bone Marrow.
DR. RUNDLES.
12:30– 1:00 Treatment of Hodgkin's Disease.
DR. HUGULEY.

P.M. Session

2:00– 4:00 Laboratories on Sixth Floor of Jefferson Hospital for microscopic work, lantern slide demonstrations, and examination of patients by Officers of Instruction and Visiting Faculty.

Thursday, December 8

HEMORRHAGIC DISEASES

A.M. Session

9:00– 9:30 Modern Concepts on Coagulation of the Blood.
DR. FROMMEYER.
9:30–10:00 Diagnosis of Hemorrhagic Diseases.
DR. DIGGS.
10:00–10:30 Hereditary Hemorrhagic Telangiectasis.
DR. STOKES.

10:30–11:00 Treatment of Hemorrhagic Diseases.
DR. DIGGS.

11:00–11:30 The Problem of Hypersplenism.
DR. KRACKE.

11:30–12:00 Surgical Aspects of Portal Hypertension.
DR. CHENOWETH.

12:00– 1:00 Clinico-pathological Conference.
DRS. JONES and BAKER.

P.M. Session

2:00– 4:00 Laboratories on Sixth Floor of Jefferson Hospital for microscopic work, lantern slide demonstrations, and examination of patients by Officers of Instruction and Visiting Faculty.

Friday, December 9

MISCELLANEOUS

A.M. Session

9:00– 9:30 The Inheritance of Blood Diseases.
DR. BUTTERWORTH.

9:30–10:00 Biopsy of the Liver.
DR. RUNDLES.

10:00–10:30 Recent Advances in Transfusion Therapy.
DR. BROWN.

10:30–11:00 Evaluation of Bone Marrow Patterns.
DR. RISER.

11:00–11:30 The Inheritance of Red Cell Agglutinogens.
DR. BUTTERWORTH.

11:30–12:00 Practical Aspects of the Rh Problem.
DR. BROWN.

12:00–12:30 Tests for Malignancy as Applied to Hematology.
DR. CLINE.

12:30– 1:00 Primary and Secondary Polycythemia.
Dr. RISER.

P.M. Session

2:00– 4:00 Laboratories on Sixth Floor of Jefferson Hospital for microscopic work, lantern slide demonstrations, and examination of patients by Officers of Instruction and Visiting Faculty.

Note: Discussions of all morning papers will take place during the Afternoon Sessions.

Saturday, December 10

SOUTHEASTERN REGIONAL MEETING OF THE AMERICAN COLLEGE OF PHYSICIANS

The Annual Regional Meeting of the Southeastern States and Cuba will be held at Birmingham and the program is offered as an integral part of this postgraduate course.

COURSE NO. 8—THE PHYSIOLOGIC APPROACH TO CLINICAL PROBLEMS IN THE CARDIOVASCULAR DISEASES

(December 5–10, 1949)

THE UNIVERSITY OF SOUTHERN CALIFORNIA SCHOOL OF MEDICINE
1200 N. STATE ST., LOS ANGELES, CALIF.

GEORGE C. GRIFFITH, M.D., F.A.C.P., *Director*

(Minimal Registration, 50;
Maximal Registration, 125)

Fees: A.C.P. Members, $30.00
V. A. (P. L. 346), $30.00
Non-members, $60.00

Consulting Committee

PHOEBUS BERMAN, M.D.
LEWIS T. BULLOCK, M.D.
JAMES F. CHURCHILL, M.D., F.A.C.P.
LELAND P. HAWKINS, M.D., F.A.C.P.
B. O. RAULSTON, M.D., F.A.C.P.
EDWARD C. ROSENOW, JR., M.D., F.A.C.P.
PAUL STARR, M.D., F.A.C.P.
HOWARD F. WEST, M.D., F.A.C.P.

OFFICERS OF INSTRUCTION

JOHN MARTIN ASKEY, M.D., F.A.C.P., Assistant Clinical Professor of Medicine, University of Southern California School of Medicine.

PHOEBUS BERMAN, M.D., Associate Clinical Professor of Medicine, University of Southern California School of Medicine; Medical Director, Los Angeles County Hospital.

ROBERT I. BOYD, M.D., Instructor in Medicine, University of Southern California School of Medicine.

THOMAS H. BREM, M.D., Instructor in Medicine, University of Southern California School of Medicine.

JAMES H. BRITTON, M.D., Instructor in Medicine, University of Southern California School of Medicine.

LEWIS T. BULLOCK, M.D., Assistant Clinical Professor of Medicine, University of Southern California School of Medicine.

EDWARD M. BUTT, M.D., Professor of Pathology, University of Southern California School of Medicine.

GURTH CARPENTER, M.B., M.R.C.P., Associate Clinical Professor of Medicine, University of Southern California School of Medicine.

RAY A. CARTER, M.D., F.A.C.R., Professor of Radiology, University of Southern California School of Medicine.

ROBERT CLELAND, M.D., Instructor in Pediatrics, University of Southern California School of Medicine.

SEYMOUR L. COLE, M.D., Instructor in Medicine, University of Southern California School of Medicine.

ELIOT CORDAY, M.D., Guest Lecturer. Institute for Medical Research, Cedars of Lebanon Hospital.

MARVIN B. CORLETTE, M.D., F.A.C.P., Instructor in Medicine, University of Southern California School of Medicine.

RICHARD S. COSBY, M.D., Assistant Clinical Professor of Medicine, University of Southern California School of Medicine.

MARVIN DARSIE, M.D., Research Associate in Surgery, University of Southern California School of Medicine.

SIM P. DIMITROFF, M.D., Instructor in Medicine, University of Southern California School of Medicine.

DOUGLAS R. DRURY, M.D., Professor of Physiology, University of Southern California School of Medicine.

DONALD T. EDMEADES, M.D., Assistant Clinical Professor of Medicine, University of Southern California School of Medicine.

HUGH A. EDMONDSON, M.D., Professor of Pathology, University of Southern California School of Medicine.

STEPHEN R. ELEK, M.D., Instructor in Medicine, University of Southern California School of Medicine.

EDWARD R. EVANS, M.D., Assistant Clinical Professor of Medicine, University of Southern California School of Medicine.

H. RUSSELL FISHER, M.D., F.A.C.P., Professor of Pathology, University of Southern California School of Medicine.

HARRY GOLDBLATT, M.D., Professor of Pathology, University of Southern California School of Medicine.

GEORGE C. GRIFFITH, M.D., F.A.C.P., Clinical Professor of Medicine, University of Southern California School of Medicine.

ERNEST M. HALL, M.D., F.A.C.P., Professor of Pathology, University of Southern California School of Medicine.

ARTHUR M. HOFFMAN, M.D., F.A.C.P., Associate Clinical Professor of Medicine, University of Southern California School of Medicine.

RALPH E. HOMANN, JR., M.D., Assistant Professor of Medicine, University of Southern California School of Medicine.

ROBERT W. HUNTINGTON, JR., M.D., Associate Professor of Pathology, University of Southern California School of Medicine.

JOHN C. JONES, M.D., F.A.C.S., Associate Clinical Professor of Surgery, University of Southern California School of Medicine.

JULIUS KAHN, M.D., Associate Clinical Professor of Medicine, University of Southern California School of Medicine.

DAVID C. LEVINSON, M.D., Research Associate, Department of Cardiology, University of Southern California School of Medicine.

MOREY L. LIPKIS, M.D., Instructor in Medicine, University of Southern California School of Medicine.

ALBERTO MARIANACCI, M.D., Head, Electro-encephalography Department, Los Angeles County Hospital.

HELEN E. MARTIN, M.D., Associate Professor of Medicine, University of Southern California School of Medicine.

LOUIS E. MARTIN, M.D., F.A.C.P., Associate Clinical Professor of Medicine, University of Southern California School of Medicine.

VERNE R. MASON, M.D., Clinical Professor of Medicine, University of Southern California School of Medicine.

EDGAR F. MAUER, M.D., Assistant Clinical Professor of Medicine, University of Southern California School of Medicine.

PERRY J. MELNICK, M.D., F.A.C.P., Associate Professor of Pathology, University of Southern California School of Medicine.

HAROLD MILLER, M.D., Fellow, Department of Cardiology, University of Southern California School of Medicine.

HYMAN MILLER, M.D., Associate Clinical Professor of Medicine, University of Southern California School of Medicine.

William J. Mitchell, M.D., F.A.C.P., Assistant Clinical Professor of Medicine, University of Southern California School of Medicine.

Frederick W. S. Modern, M.D., F.A.C.P., Associate Clinical Professor of Medicine, College of Medical Evangelists.

Frederick J. Moore, M.D., Associate Professor of Medicine (Experimental), University of Southern California School of Medicine.

Jackson Norwood, M.D., Assistant Clinical Professor of Medicine, University of Southern California School of Medicine.

Griffith D. Page, M.D., Instructor in Medicine, University of Southern California School of Medicine.

Harold E. Pearson, M.D., Associate Professor of Bacteriology and Parasitology, University of Southern California School of Medicine.

Donald W. Petit, M.D., Assistant Professor of Medicine, University of Southern California School of Medicine.

Edward Phillips, M.D., Instructor in Medicine, University of Southern California School of Medicine.

Myron Prinzmetal, M.D., Senior Attending Physician and Director of Beaumont Laboratories for Cardiovascular Disease, Cedars of Lebanon Hospital.

Guy E. Radar, M.D., Resident in Pediatrics, Los Angeles County Hospital.

B. O. Raulston, M.D., F.A.C.P., Dean and Professor of Medicine, University of Southern California School of Medicine.

Edward C. Rosenow, Jr., M.D., F.A.C.P., Associate Professor of Medicine and Director, Medical Extension Education, University of Southern California School of Medicine.

John P. Sampson, M.D., F.A.C.P., Assistant Clinical Professor of Medicine, University of Southern California School of Medicine.

Joseph M. Shachtman, M.D., Instructor in Medicine, University of Southern California School of Medicine.

Edward Shapiro, M.D., Assistant Clinical Professor of Medicine, University of Southern California School of Medicine.

Jack A. Sheinkopf, M.D., Instructor in Medicine, University of Southern California School of Medicine.

Paul Starr, M.D., F.A.C.P., Professor of Medicine, University of Southern California School of Medicine.

Clinton H. Thienes, M.D., Professor of Pharmacology and Toxicology, University of Southern California School of Medicine.

William Paul Thompson, M.D., Associate Professor of Medicine, College of Medical Evangelists.

Meyer C. Thorner, M.D., Instructor in Medicine, University of Southern California School of Medicine.

Richard F. Webb, M.D., Instructor in Medicine, University of Southern California School of Medicine.

Sidney Weisman, M.D., Instructor in Medicine, University of Southern California School of Medicine.

Howard F. West, M.D., F.A.C.P., Clinical Professor of Medicine, University of Southern California School of Medicine.

Travis W. Winsor, M.D., F.A.C.P., Instructor in Medicine, University of Southern California School of Medicine.

Anton S. Yuskis, M.D., Instructor in Medicine, University of Southern California School of Medicine.

Willard J. Zinn, M.D., Fellow, Department of Cardiology, University of Southern California School of Medicine.

The physiologic approach to the clinical problems in cardiovascular disease will be the basis of the week's study. Individual symptoms, physical signs and diagnostic

technics will be discussed from the physiologic and clinical standpoints. Roentgenology, electrocardiography and cardiac catheterization will be presented from the primary viewpoint of the underlying altered physiology.

Five clinical pathological conferences will emphasize the differential diagnosis of heart disease. There will be five clinical sessions in which cases illustrating physiologic problems such as dyspnea, cyanosis, pain, edema and heart failure will be studied.

The technic and value of cardiac catheterization, anticoagulants, and newer therapeutic trends will be fully covered.

Hotel Accommodations: The Biltmore Hotel, Mr. Francis Bustillo, Convention Manager, Los Angeles 13, Calif. Rates: Single rooms, $7.00–$8.00 daily; double or twin-bedded rooms, $13.50 daily.

Alexandria Hotel, Mr. Frank Walker, General Manager, 5th and Spring Sts., Los Angeles 13, Calif. Rates: Single rooms with bath, $5.00–$6.00 daily; double rooms with bath, $7.50 daily; twin-bedded rooms with bath, $8.50 daily.

The above hotels are located near one another and are equally convenient to the meeting place of the course. In making reservations, identify yourself with The American College of Physicians and this particular course.

Outline of Course

Monday, December 5

A.M. Session

9:00– 9:15 Registration.

9:15– 9:30 Orientation.
B. O. Raulston, M.D., Dean, School of Medicine.
Phoebus Berman, M.D., Medical Director, Los Angeles County Hospital.

9:30– 9:50 Physiology of Dyspnea.
Dr. Homann.

9:50–10:05 Clinical Aspects of Dyspnea.
Dr. Norwood.

10:05–10:20 The Mechanism and Radiation of Coronary Artery Pain.
Dr. Griffith.

10:20–10:40 Differential Diagnosis of Chest Pain.
Dr. Cosby.

10:40–11:00 The Physiologic Basis of Drugs Used in Coronary Pain.
Dr. Elek.

11:00–11:20 The Prevention and Rehabilitation of Coronary Thrombosis.
Dr. Kahn.

11:20–12:00 New Instrumentation in Cardiovascular Physiology.
Dr. Drury.

P.M. Session

1:00– 2:00 Clinical Pathological Conference.
Drs. Edmondson and Mason.

2:00– 3:00 Pain Clinic.

Case—Parietal Pain.
Dr. Griffith.
Case—Coronary Insufficiency.
Dr. Rosenow.
Case—Acute Myocardial Infarction.
Dr. Sheinkopf.
Case—Dissecting Aneurysm of the Aorta.
Dr. Edmeades.

3:00– 3:20 Differential Diagnosis and Treatment of Cardiac and Bronchial Asthma.
Dr. Hyman Miller.
3:20– 4:00 Metabolism of Heart Muscle and the Effects of Drugs on Same.
Dr. Thienes.

Tuesday, December 6

A.M. Session

9:00– 9:30 Physiology of Congestive Heart Failure.
Dr. Homann.
9:30–10:05 Treatment of Congestive Failure.
Dr. Corlette.
10:05–10:20 Physiology of Cyanosis.
Dr. Cosby.
10:20–10:40 Differential Diagnosis of Polycythemias.
Dr. Carpenter.
10:40–11:00 Effects of Anemia and Polycythemia on the Cardiovascular System.
Dr. Evans.
11:00–11:20 The Significance of Clubbed Fingers.
Dr. Mauer.
11:20–11:40 The Mechanism of Cardiac Murmurs in Anemia.
Dr. Shapiro.
11:40–12:00 Phonocardiography in Heart Disease.
Dr. Schachtman.

P.M. Session

1:00– 2:00 Clinical Pathological Conference.
Drs. Hall and Hoffman.
2:00– 3:00 Heart Failure Clinic.

Case—Pure Left Heart Failure.
Dr. Phillips.
Case—Primary Right Heart Failure.
Dr. Dimitroff.
Case—Congestive Failure.
Dr. Webb.
Case—Constrictive Pericarditis with Edema.
Dr. Levinson.

3:00–3:20 Low Sodium Intake.
Dr. Cole.
3:20– 3:40 Pharmacology of Digitalis and Choice of Preparation.
Dr. Sheinkopf.
3:40– 3:50 Digitalis Intoxication.
Dr. Britton.
3:50– 4:00 Cerebral Manifestations of Digitalis.
Drs. Harold Miller and Marianacci.

Wednesday, December 7

A.M. Session

9:00– 9:20 History, Purpose and Technic of Cardiac Catheterization.
Dr. Griffith.
9:20– 9:40 X-Ray in Cardiac Catheterization.
Dr. Carter.
9:40–10:05 Oxygen Studies in Cardiac Catheterization.
Dr. Darsie.

10:05–10:20 Acyanotic Heart Disease in Cardiac Catheterization.
Dr. Levinson.
10:20–10:40 Cyanotic Heart Disease in Cardiac Catheterization.
Dr. Cosby.
10:40–10:50 Electrocardiogram during Cardiac Catheterization.
Dr. Zinn.
10:50–11:00 Summary of Studies.
Dr. Griffith.
11:00–12:00 Cardiac Arrhythmias.
Drs. Prinzmetal and Corday, and Staff.

P.M. Session

1:00– 2:00 Clinical Pathological Conference.
Drs. Huntington and Louis E. Martin.
2:00– 3:00 Rheumatic Heart Disease.

Case—Rheumatic Fever.
Dr. Griffith.
Case—Mitral Stenosis with Auricular Fibrillation.
Dr. Askey.
Case—Aortic Insufficiency and Mitral Stenosis.
Dr. Lipkis.

3:00–3:30 Etiology and Pathogenesis of Rheumatic Fever.
Dr. Griffith.
3:30– 4:00 The Diagnosis of Rheumatic Fever.
Dr. Martin.

Thursday, December 8

A.M. Session

9:00– 10:30 Humoral Mechanism of Hypertension.
Dr. Goldblatt.
10:30–10:45 Early Renal Lesions Predisposing Hypertension.
Dr. Boyd.
10:45–11:00 Psychic Aspects of Hypertension.
Dr. Page.
11:00–12:00 Clinical Electrocardiographic Pathologic Conference.
Dr. Thompson.

P.M. Session

1:00– 2:00 Clinical Pathological Conference.
Drs. Fisher and Helen E. Martin.
2:00– 2:30 Congenital Clinic.

Case—Patent Ductus Arteriosus.
Dr. Griffith.
Case—Coarctation of Aorta.
Dr. Brem.
Case—I. A. Septal Defect.
Dr. Cosby.
Case—Tetralogy of Fallot.
Dr. Cleland.

2:30– 3:00 The Differential Diagnosis of Congenital Heart Disease.
Dr. Martin.
3:00– 4:00 Surgery of Congenital Heart Disease.
Dr. Jones.

Friday, December 9

A.M. Session

9:00–10:05 The Physiologic Implications Obtained from Roentgenologic Study of the Thorax.
DR. CARTER.

10:05–10:20 Rupture of the Heart in Myocardial Infarction.
DR. ASKEY.

10:20–10:40 Diphtheritic Myocarditis.
DR. MITCHELL.

10:40–11:00 Some Interesting Cardiac Effects of Certain Primary Extra Cardiac Disturbances.
DR. PETIT.

11:00–11:20 Heavy Metal Deposition in Various Organs.
DR. BUTT.

11:20–11:40 Laboratory Aspects of the Diagnosis and Treatment of Bacterial Endocarditis.
DR. PEARSON.

11:40–12:00 Effects of Blood Sugar Variations on the Heart and Circulation.
DR. WEST.

P.M. Session

1:00– 2:00 Clinical Pathological Conference.
DRS. MELNICK and BULLOCK.

2:00– 2:15 Orthostatic Hypotension.
DR. YUSKIS.

2:15– 2:30 Treatment of Shock in Acute Myocardial Infarction.
DR. WEISMAN.

2:30– 2:45 Physiologic Effects of Arteriovenous Aneurysm on the Heart.
DR. COSBY.

2:45– 3:15 The Heart in Thyroid Disease.
DR. STARR.

3:15– 3:30 Nutritional Heart Disease.
DR. MODERN.

3:30– 4:00 Anticoagulants in Cardiovascular Disease.
DR. GRIFFITH.

Saturday, December 10

A.M. Session

9:00–10:05 Electrocardiograms.
Questions and Answers.
DR. WINSOR.

10:05–10:20 The Q T Interval as a Diagnostic and Treatment Aid in Acute Myocarditis.
DR. THORNER.

10:20–10:40 Therapeutic Hazards in Cardiac Emergencies.
DR. HOFFMAN.

10:40–11:00 Morphine in Cardiac Disease.
DR. SAMPSON.

11:00–11:30 The Adrenergic and Anti-adrenergic Drugs.
DR. THIENES.

11:30–12:00 Adrenal Corticotropic Hormone and Compound E in Rheumatic Disease.
DR. MOORE.

All registrations must be entered through the central office of The American College of Physicians, 4200 Pine St., Philadelphia 4, Pa.

The registration in other courses, now completed, on the Autumn program of the College was gratifying, attesting to the continued popularity of these excellent courses. The 1950 schedule is being prepared by the Advisory Committee on Postgraduate Courses and will be announced in the next issue of this journal.

Regional Meetings

Reports on Recent Meetings

Eastern Canada and New England—Montreal, September 23–24, 1949. This was a two-day Regional Meeting covering the New England States, the Maritime Provinces and the Province of Quebec. Dr. Arthur T. Henderson, F.A.C.P., Governor for Quebec, was General Chairman; Dr. E. H. Mason, F.A.C.P. was Chairman of the Committee on Arrangements, and Dr. J. S. L. Browne, F.A.C.P. was Chairman of the Program Committee. Governors of the participating New England States and the Maritime Provinces coöperated and an attempt was made to have speakers from each State or Province. The various Governors presided over different portions of the program. All meetings were held at the Windsor Hotel, but the last afternoon was given over to visits to the Institute of Experimental Medicine and Surgery at the University of Montreal, to the Osler Library of McGill University and to the Montreal General Hospital Institute for Special Research and Cell Metabolism. The program was as follows:

Friday Morning Session

Presiding Officer

Chester S. Keefer, M.D., F.A.C.P.

Governor for Massachusetts

9:30–10:30 Adaptation Syndrome.
Hans Selye, M.D., Ph.D. (by invitation), Director, Institute of Experimental Medicine and Surgery, Université de Montreal, and J. S. L. Browne, M.D., F.A.C.P., Professor of Medicine, McGill University, Montreal, P. Q.

10:30–11:00 Coronary Sclerosis and Pulmonary Hypertension.
Eugene H. Drake, M.D., F.A.C.P., Portland, Maine.

11:00–11:30 Recent Developments in the Pathogenesis of Diabetes Mellitus.
Martin M. Hoffman, M.D., Ph.D. (by invitation), Assistant Professor of Medicine, McGill University, Montreal, P. Q.

11:30–12:00 Shunting of Cerebrospinal Fluid into Peritoneal Cavity.
W. V. Cone, M.D. (by invitation), Associate Professor of Neurosurgery, McGill University,
Revis Lewis, M.D. (by invitation), and
Ira Jackson, M.D. (by invitation); Montreal, P. Q.

Afternoon Session

Presiding Officer

Herman A. Lawson, M.D., F.A.C.P.

Governor for Rhode Island

2:00– 2:30 The Use of Radioactive Isotopes in Medical Investigation and Treatment.
Joseph P. Ross (by invitation), Boston, Mass.

2:30– 3:00 The Function and Value of Hospital Diet Committees.
E. H. BENSLEY, M.D. (by invitation), Director of the Department of Metabolism and Toxicology, Montreal General Hospital, Montreal, P. Q.

3:00– 3:30 The Metabolism of Thiocyanates after Prolonged Administration in Man.
F. C. MOISTER, M.D. (by invitation), and
EDWARD D. FREIS, M.D. (by invitation); Hanover, N. H.

3:30– 3:45 INTERMISSION.

3:45– 4:15 Recent Advances in Neurology.
FRANCIS MCNAUGHTON, M.D. (by invitation), Associate Professor of Neurology, McGill University, Montreal, P. Q.

4:15– 4:45 Tension and Health.
D. EWEN CAMERON, M.D. (by invitation), Director, Allan Memorial Institute, and Professor of Psychiatry, McGill University, Montreal, P. Q.

EVENING

6:30 Cocktails.

7:15 Dinner (Informal).
Toastmaster: CHARLES F. MOFFATT, M.D., F.A.C.P., Regent, American College of Physicians, Montreal, P. Q.
Addresses: REGINALD FITZ, M.D., F.A.C.P., President, American College of Physicians, Boston, Mass.
E. R. LOVELAND, Executive Secretary, American College of Physicians, Philadelphia, Pa.

SATURDAY MORNING SESSION

Presiding Officer

HARRY T. FRENCH, M.D., F.A.C.P.

Governor for New Hampshire

9:00–10:00 PANEL DISCUSSION: Chronic Pulmonary Disease.
J. C. MEAKINS, M.D., M.A.C.P., Chairman.
G. W. WRIGHT, M.D. (by invitation), Trudeau Sanatorium, Saranac Lake, N. Y.
N. D'ESOPO, M.D. (by invitation), Veterans Administration Hospital, Sunmount, N. Y.
HUGH BURKE, M.D. (by invitation), Royal Edward Laurentian Hospital, Montreal, P. Q.
C. A. MCINTOSH, M.D. (by invitation), Royal Victoria Hospital, Montreal, P. Q.
HUGH STARKEY, M.D. (by invitation), In charge of Veteran Affairs, Queen Mary Hospital, Montreal, P. Q.

10:00–10:30 *B. Coli* Ulcerative Endocarditis.
L. C. STEEVES, M.D. (by invitation), Halifax, N. S.

10:30–11:00 Thyrotoxicosis: Newer Aspects.
E. B. ASTWOOD, M.D., F.A.C.P., Research Professor of Medicine, Tufts College Medical School, Boston, Mass.

11:00–11:15 INTERMISSION.

11:15–11:45 Results of the Treatment of Hypertensive Vascular Disease by Sodium Restriction.
MICHAEL DIMAIO, M.D. (by invitation), Providence, R. I.

11:45–12:15 Rickettsial Pox.
JOHN F. DALY, M.D. (by invitation), Assistant Professor of Dermatology, University of Vermont, Burlington, Vt.

Papers, 20 minutes; 10 minutes for discussion.

Western New York—Buffalo, October 1, 1949. The Western New York Regional Meeting has been established over many years, and has grown to be a popular and exceedingly well-attended meeting. Enthusiasm is always high and attendance is exceptionally good. The meeting was held under the Governorship of Dr. Edward C. Reifenstein, F.A.C.P., Syracuse. Dr. Edward F. Driscoll, F.A.C.P., Buffalo, was Chairman of the Committee on Arrangements and Dr. Roy L. Scott, F.A.C.P., Buffalo, was Chairman of the Scientific Program Committee. All sessions were held at the Hotel Statler. 118 members and 73 guests were registered. The program was as follows:

MORNING SESSION

NELSON G. RUSSELL, SR., M.D., F.A.C.P.,

Buffalo, N. Y.

Presiding

9:30 Liver Biopsy.
DRS. A. H. AARON, F.A.C.P., KORNEL TERPLAN, S. SANES, W. F. LIPP, W. H. CHAPPLE, A. R. LENZNER, and R. C. BAHN; Buffalo, N. Y.

9:50 The Use of Tetraethylthiuramdisulphide (Antabuse) in the Rehabilitation of the Alcoholic.
DRS. KENNETH GOLDSTEIN (Associate), L. OSBORNE, R. KIDDER, W. CORCORAN, and R. HUBBARD; Buffalo, N. Y.

10:10 Some Aspects of the Epidemiologic Problems of Rocky Mountain Spotted Fever on Long Island.
DR. JOHN K. MILLER (Associate), Albany, N. Y.

10:30 Coarctation of the Aorta.
DRS. NELSON G. RUSSELL, JR., F.A.C.P., and JOHN R. PAINE (by invitation); Buffalo, N. Y.

10:50 INTERMISSION.

RICHARD N. DENIORD, M.D., F.A.C.P.,

Buffalo, N. Y.

Presiding

11:00 Advances in Electrocardiography.
DR. GEORGE H. REIFENSTEIN (Associate), Syracuse, N. Y.

11:20 The Vascular Menace in Diabetes.
DR. CHARLES B. F. GIBBS, F.A.C.P., Rochester, N. Y.

11:40 Discussion by DR. REGINALD FITZ, Boston, Mass.

12:00 INTERMISSION.

12:30 LUNCHEON (Terrace Room).

AFTERNOON SESSION

MAYNARD E. HOLMES, M.D., F.A.C.P.,

Syracuse, N. Y.

Presiding

2:20 Results of Treatment of Minimal Active Tuberculosis with Modified Bed Rest.
DR. ROGER S. MITCHELL, JR., F.A.C.P., Trudeau, N. Y.

2:40 The Prevention of Diabetes.
DR. BERNARD A. WATSON, F.A.C.P., Clifton Springs, N. Y.

3:00 The Rôle of the Internist in Rehabilitation.
DR. JOHN M. NICKLAS, F.A.C.P., Saranac Lake, N. Y.

3:20 Production of Artificial Jaundice in the Investigation of Rheumatoid Arthritis.
DRS. B. M. NORCROSS (Associate), L. M. LOCKIE, SR., F.A.C.P., and J. H. TALBOTT, F.A.C.P., Buffalo, N. Y.

3:40 The Effects of Respiration on the Circulation in Relation to Angina Pectoris and Circulatory Failure.
DR. WILLIAM S. MCCANN, F.A.C.P., Rochester, N. Y.

4:00 INTERMISSION.

DR. PAUL C. CLARK, F.A.C.P., Syracuse, N. Y.

Presiding

4:10 Demonstration of Diagnostic Cells in Disseminated Lupus Erythematosus.
DR. S. L. VAUGHAN, F.A.C.P., Buffalo, N. Y.

4:20 Familial Incidence of Disseminated Lupus Erythematosus.
DR. WILLARD H. WILLIS, F.A.C.P., Utica, N. Y.

4:30 Idiopathic Pulmonary Fibrosis; Case Report.
DR. R. E. SMITH (Associate), Clifton Springs, N. Y.

4:40 CLINICAL PATHOLOGICAL CONFERENCE.
DR. KORNEL TERPLAN, Pathologist, Buffalo, N. Y. (by invitation).
Discusser: DR. W. WALTER STREET, F.A.C.P., Syracuse, N. Y.

A reception and banquet were held in the evening with Dr. A. H. AARON, F.A.C.P. as Toastmaster and with the following distinguished guests:

DR. REGINALD FITZ, F.A.C.P., Boston, Mass., President, The American College of Physicians.

DR. WILLIAM S. MCCANN, F.A.C.P., Rochester, N. Y., Regent, The American College of Physicians.

MR. EDWARD R. LOVELAND, Philadelphia, Pa., Executive Secretary, The American College of Physicians.

DR. NELSON G. RUSSELL, SR., F.A.C.P., Former Governor for Western New York.

DR. HERBERT K. DETWEILER, F.A.C.P., Toronto, Ont., Governor for the Province of Ontario.

DR. RAY F. FARQUHARSON, F.A.C.P., Professor of Medicine, University of Toronto Faculty of Medicine.

DR. EDWARD C. REIFENSTEIN, F.A.C.P., Syracuse, N. Y., Governor for Western New York.

Mississippi—Jackson, October 8, 1949. This regional meeting was held under the Governorship of Dr. John G. Archer, F.A.C.P., Greenville, with Dr. Gayden

Ward, F.A.C.P., acting as Chairman of the Entertainment Committee. The College membership in Mississippi is comparatively small but it is customary for every member to turn out for the annual Regional Meeting there. Their program was as follows:

Presiding

JOHN G. ARCHER, B.S., M.D., F.A.C.P.

Greenville, Mississippi

Governor for Mississippi

The Internist's Responsibility for the Elderly Surgical Patient.
W. K. PURKS, M.D., F.A.C.P., Vicksburg, Mississippi.
Coarctation of Aorta With Report of Two Cases Operated upon Successfully.
GAYDEN WARD, M.D., F.A.C.P.
GEORGE HARVEY, JR., M.D. (by invitation), Jackson, Mississippi.
Prognosis of Heart Disease.
BEN R. HENINGER, M.D., F.A.C.P., Gulfport, Mississippi.
Management of Congestive Heart Failure.
SAMUEL NADLER, M.D., F.A.C.P., Associate Professor of Clinical Medicine, Tulane University, New Orleans, Louisiana.
Psychosomatic Medicine.
JAMES F. LEWIS, M.D., F.A.C.P., Columbus, Mississippi.
Amyloid Disease.
DOUGLAS D. BAUGH, M.D., F.A.C.P., Columbus, Mississippi.
Lower Nephron Nephrosis. (*Acute Renal Failure.*)
WESLEY W. LAKE, M.D., F.A.C.P., Pass Christian, Mississippi.
The Problem of Hypersplenism.
ROY KRACKE, M.D. (by invitation), Dean, Medical College of Alabama, Birmingham, Alabama.
SOCIAL HOUR.
BANQUET (INFORMAL).
Toastmaster—MR. GEORGE GODWIN, Jackson, Mississippi.
Speaker—GOV. FIELDING WRIGHT, Governor of Mississippi.

Puerto Rico—Santurce, October 16, 1949. This was the first Regional Meeting ever formally organized in Puerto Rico. Dr. Rafael Rodriguez-Molina, F.A.C.P., as the Governor for the Island, organized the meeting and former President, Hugh J. Morgan, F.A.C.P., was the special representative from the Board of Regents. The program was as follows:

PROGRAM

Presiding Officer

RAMON M. SUAREZ, M.D., F.A.C.P., San Juan

Bleeding Tendency Due to Circulating Anticoagulants, with Report of a Case.
EDUARDO R. PONS, JR., M.D. (by invitation), and MERCEDES VICENTE DE TORREGROSA, Ph.D. (by invitation), San Juan City Hospital.
Pathogenesis of Schistosomiasis with Special Reference to Schistosomal Cirrhosis.
ENRIQUE KOPPISCH, M.D., F.A.C.P., Acting Director and Professor of Pathology, School of Tropical Medicine, San Juan.

The Present Status of the Intradermal Reaction in the Diagnosis of Schistosomiasis and Filariasis.

Jose Oliver-Gonzalez, Ph.D. (by invitation), Associate Professor of Medical Zoölogy, School of Tropical Medicine, San Juan.

Myocarditis.

Hugh J. Morgan, M.D., D.Sc., F.A.C.P., Regent and Former President, The American College of Physicians; Professor of Medicine, Vanderbilt University School of Medicine; Physician-in-Chief, Vanderbilt University Hospital; Nashville, Tenn.

Incidence of Hypertension in Puerto Rico.

Ramon M. Suarez, M.D., F.A.C.P., Director, Mimiya Hospital; Consultant in Medicine, Veterans Administration Center, San Patricio Hospital; San Juan.

Electrocardiographic Changes in Phosphorus Poisoning.

Rurico S. Diaz-Rivera, M.D., F.A.C.P., Chief, Medical Service, San Juan City Hospital.

Treatment of Amebiasis with A.D. 4712.

Federico Hernandez-Morales, M.D., F.A.C.P., Associate Professor of Tropical Medicine, School of Tropical Medicine, and Enrique Perez-Santiago, M.D. (by invitation), Medical Supervisor, University Hospital, San Juan.

Meningitis in Infants and Children in Puerto Rico.

Antonio Ortiz-Ortiz, M.D., F.A.C.P., Chief, Pediatric Service, San Juan City Hospital.

Hypercholesteremia and Its Relation to Coronary Artery Disease.

Roberto Francisco Azize, M.D., F.A.C.P., Director, San Juan Diagnostic Clinic.

Evening

Condado Beach Hotel

8:30 Dinner (Formal).

Presiding Officer

Rafael Rodriguez-Molina, M.D., F.A.C.P.

Governor of The American College of Physicians; Chief, Medical Service, San Patricio Hospital, Veterans Administration Center; Assistant Professor of Tropical Medicine, School of Tropical Medicine; San Juan, P. R.

Address

Dr. Hugh J. Morgan, Nashville, Tenn.

Regent and Former President of The American College of Physicians

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Arizona—Phoenix, October 22, 1949. Dr. Leslie R. Kober, F.A.C.P., as Governor for Arizona, organized and directed the meeting. Dr. Joseph Bank, F.A.C.P., and Dr. Hilton J. McKeown, F.A.C.P., both of Phoenix, were Chairmen of the Program Committee and the Arrangements Committee, respectively. This was the first Arizona Regional Meeting of the College. The Arizona membership numbers but 43, but the great majority were in attendance and brought with them a number of guests who were interested in the College and the program. It is anticipated that the success of this meeting will result in annual clinical programs of increasing value and importance to the medical profession in Arizona. Their program was as follows:

PROGRAM

Panel Discussion: Climatic Influence on Disease.
Climate and Respiratory Diseases.
KENT H. THAYER, M.D., F.A.C.P., Phoenix.
Climate and Metabolic Disturbances.
LESLIE B. SMITH, M.D., F.A.C.P., Phoenix.
Climate and Rheumatic Diseases.
HARRY E. THOMPSON, M.D., F.A.C.P., Tucson.
Discussion.
Early Diagnosis of Cor Pulmonale.
GEORGE C. GRIFFITH, M.D., F.A.C.P., Clinical Professor of Medicine, University of Southern California, Los Angeles, California.
Biochemical Studies in Demyelinating Disease.
HAROLD H. JONES, M.D., F.A.C.P., Regent and Former Governor for Kansas of The American College of Physicians, Winfield, Kansas.
Recent Advances in The Treatment of Arthritis.
W. PAUL HOLBROOK, M.D., F.A.C.P., President, The Arthritis and Rheumatism Foundation, and DONALD F. HILL, M.D., F.A.C.P., Tucson.
Lower Abdominal Aneurysms.
LOUIS B. BALDWIN, M.D., F.A.C.P., Phoenix.
Non-tuberculous Intra-thoracic Lesions.
HAROLD KOHL, SR., M.D. (Associate), Tucson.
Necrotizing Arteritis Resulting from Generalized Fungus Infection.
ONIE O. WILLIAMS, M.D. (Associate), Director of the Clinical Laboratory and Pathologist, St. Joseph's Hospital, Phoenix.
Indications for Thoracotomy.
HOWELL S. RANDOLPH, M.D., F.A.C.P., Phoenix.

EVENING

RECEPTION AND COCKTAILS.
DINNER (INFORMAL).
Toastmaster: ROBERT S. FLINN, M.D., F.A.C.P., Phoenix, President, Arizona State Medical Association.
Distinguished Guest Speakers:
HAROLD H. JONES, M.D., F.A.C.P., Regent, Winfield, Kansas. "The American College of Physicians—Present Trends."
GEORGE C. GRIFFITH, M.D., F.A.C.P., Clinical Professor of Medicine, University of Southern California, Los Angeles, California. "Physiological Findings in Arteriovenous Aneurysms by Cardiac Catheterization Methods."

Midwest Regional Meeting—Indianapolis, November 19, 1949. Dr. J. O. Ritchey, F.A.C.P., Governor for Indiana, General Chairman, with the coöperation of the College Governors for Illinois, Iowa, Michigan, Minnesoto, Ohio and Wisconsin. Dr. William S. Middleton, F.A.C.P., Madison, Wis., President-Elect, A.C.P., was the chief speaker at the banquet. Copy of the program is not available at the time this copy goes to press.

New Jersey Regional Meeting—Newark, November 30, 1949. Dr. George H. Lathrope, F.A.C.P., Governor for New Jersey, General Chairman; Dr. Johannes F. Pessel, F.A.C.P., Trenton, Chairman of the Program Committee; Dr. Jerome G. Kauf-

man, F.A.C.P., Newark, Chairman of Arrangements. A copy of this program is not available at the time this goes to press. However, Dr. Edward A. Strecker, F.A.C.P., Philadelphia, will be a special guest speaker on the scientific program; and Dr. Reginald Fitz, F.A.C.P., Boston, President of the College; Dr. George Morris Piersol, M.A.C.P., Philadelphia, Secretary-General; Dr. William D. Stroud, F.A.C.P., Philadelphia, Treasurer; Dr. Edward L. Bortz, F.A.C.P., Philadelphia, Regent; Dr. Thomas M. McMillan, F.A.C.P., Governor for Eastern Pennsylvania; and Mr. E. R. Loveland, Executive Secretary, are among the guests.

Kentucky Regional Meeting—Louisville, December 3, 1949. Dr. J. Murray Kinsman, F.A.C.P., Governor. Dr. William S. Middleton, F.A.C.P., President-Elect, American College of Physicians, special guest speaker. Other details of the program will be published later.

North Carolina Regional Meeting—Winston-Salem, December 9, 1949. Dr. Paul F. Whitaker, F.A.C.P., Kinston, Governor for North Carolina; Dr. Edward S. Orgain, F.A.C.P., Durham, Chairman of the Program Committee. Meetings will be held in the amphitheatre of the Bowman Gray School of Medicine starting at 2 p. m. Copy of the program not available when this copy goes to press.

Southeastern Regional Meeting—Birmingham, Ala., December 10, 1949. Dr. E. Dice Lineberry, F.A.C.P., Governor for Alabama, General Chairman; Dr. Edgar G. Givhan, Jr., F.A.C.P., Chairman of Arrangements Committee. This Regional Meeting covers Alabama, Florida, Georgia, South Carolina and Cuba, and marks the first occasion at which this meeting has been held in Alabama. Dr. Reginald Fitz, F.A.C.P., Boston, President of the College, will be the special guest speaker at the banquet. Other details of the program yet to be published and sent to all members in the territory.

Eastern Pennsylvania Regional Meeting—Philadelphia, January 20, 1950. Dr. Thomas M. McMillan, F.A.C.P., Governor for Eastern Pennsylvania, General Chairman. Meeting will be initiated by a buffet luncheon at the Headquarters of the College, followed by a scientific program and a reception and dinner at the Warwick Hotel. Program will be printed later and distributed to all in the territory.

Kansas Regional Meeting—Topeka, March 17, 1950. Dr. William C. Menninger, F.A.C.P., Governor and General Chairman. Dr. Hugh J. Morgan, F.A.C.P., Regent of the College, Nashville, Tenn., special guest speaker. Program to be published and sent to all members in the territory.

The Fifteenth Annual Meeting of the Postgraduate Medical Assembly of South Texas will be held at Houston, November 29 to December 1, 1949. Among the distinguished guest speakers are Dr. Louis H. Clerf, F.A.C.P., Philadelphia, Pa., Dr. Francis M. Rackemann, F.A.C.P., Boston, Mass., and Dr. Paul D. White, F.A.C.P., Boston, Mass.

Dr. Walter E. Vest, F.A.C.P., Huntington, W. Va., has been elected President of the new West Virginia Medical Licensing Board.

Emory University School of Medicine in coöperation with the Medical Association of Georgia offers annually a week's postgraduate course in Medicine and Surgery for general practitioners. The last such course was concluded on October 14, and was well attended by practitioners, particularly from the State of Georgia. The registration fee is $10.00 for the week.

The New Jersey Fellows of the American Academy of Pediatrics in conjunction with the Medical Society of New Jersey and the New Jersey State Department of Health recently concluded a study of child health services in the State of New Jersey. The study covers county groups in New Jersey, ratio of children to physicians, distribution of children and physicians, general hospitals admitting children, location of general hospitals admitting children, child medical care in New Jersey on an average day, medical well-child conferences, distribution of health nurses and home visits, hospitals admitting polio patients, community mental hygiene clinics, etc. Dr. Harrold A. Murray, F.A.C.P., Newark, N. J., was the Study Director.

Yale University School of Medicine has initiated a series of short postgraduate courses in a coöperative program with the Connecticut State Medical Society in the Hartford Hospital. These courses are designed to give physicians an opportunity to become familiar with new knowledge, procedures, and point of view, and to assist them in practicing better medicine. Courses cover various fields of medicine and surgery.

Announcement of Van Meter Prize Award

The American Goiter Association again offers the Van Meter Prize Award of Three Hundred Dollars and two honorable mentions for the best essays submitted concerning original work on problems related to the thyroid gland. The Award will be made at the annual meeting of the Association which will be held in Houston, Texas, March 9 to 11, 1950.

The competing essays may cover either clinical or research investigations; may not exceed three thousand words in length, must be presented in English; and a typewritten, double spaced copy, in duplicate, sent to the Corresponding Secretary, Dr. George C. Shivers, 100 E. St. Vrain Street, Colorado Springs, Colorado, not later than January 15, 1950.

"The Place of Veterans Problems in Tuberculosis Control" was the subject of an address before the Southern Tuberculosis Conference at Memphis, Tennessee, September 15, 1949, by Dr. Leo V. Schneider, F.A.C.P., Chief of the Tuberculosis Control Section of the Veterans Administration, Tuberculosis Division, Washington, D. C.

Dr. J. A. Rosenkrantz (Associate) was promoted to Assistant Chief of Professional Services of the Kingsbridge Veterans Administration Hospital, Bronx, New York, during September.

Civilian Consultants Appointed to U. S. Air Force Medical Service

Dr. W. Paul Holbrook, F.A.C.P., Tucson, Arizona, and Dr. Phillip T. Knies, F.A.C.P., Columbus, Ohio, have been appointed Consultants in Internal Medicine to the U. S. Army Air Force Medical Service. Dr. Charles E. Kossmann, F.A.C.P., New York City, has been appointed as Civilian Consultant in Cardiology.

Dr. Lowell T. Coggeshall, F.A.C.P., resigned as Chairman of the Department of Medicine of the Division of Biological Sciences at the University of Chicago on July 1, in order to devote his full time to research and to the Deanship of the medical school. His successor is Dr. Wright R. Adams, Professor of Medicine and Associate Dean.

Separate surveys are being conducted by Dr. Alan Gregg, Director of Medical Science, Rockefeller Foundation, and Dr. Harman G. Weiskotten, Dean of Syracuse University College of Medicine, concerning the need for the establishment of a four-year school of medicine and dentistry in West Virginia.

Under the presidency of Dr. George E. Baker, F.A.C.P., Casper, the Wyoming State Medical Society held its annual meeting in Casper, September 12 to 14, 1949.

Dr. Howard A. Rusk, F.A.C.P., Chairman of the Department of Rehabilitation and Physical Medicine, New York University College of Medicine, has been on an extended trip to Europe to participate in teaching seminars on rehabilitation and to confer with officials of the World Health Organization in Geneva, officials of UNESCO in Paris, and to observe rehabilitation activities in England. Dr. Rusk is Consultant in Rehabilitation to the Department of Social Affairs of the United Nations.

Southwestern Medical College to Become State University

The Board of Regents of the University of Texas has announced acceptance of the offer of the Southwestern Medical Foundation to turn over the facilities of the Southwestern Medical College. Nearly one and one-half million dollars in assets were turned over to the University of Texas, and a medical branch of the University of Texas will be established in Dallas. The new school will be known as "Southwestern Medical School."

Dr. George F. Lull Receives Legion of Honor Medal

General George F. Lull, F.A.C.P., former Deputy Surgeon General of the United States Army and now General Manager and Secretary of the American Medical Association, was presented with the Legion of Honor Medal by the French Government in recognition of his activities on behalf of the French people immediately following World War II. Dr. Lull, at an earlier time, was awarded the Distinguished Service Medal in this country.

Dr. Milton L. Hobbs, F.A.C.P., Morgantown, West Virginia, has been elected Secretary-Treasurer of the Association of Pathologists of West Virginia.

Dr. Delivan A. MacGregor, F.A.C.P., Wheeling, College Governor for West Virginia, and Dr. Frank J. Holroyd, F.A.C.P., Princeton, have been appointed Chairman and Member, respectively, of a Liaison Committee between the West Virginia State Medical Association and the Board of Governors of West Virginia University. The purpose of the Committee is to establish more effective relations between the two institutions and a better understanding of the needs of the medical profession in the field of medical education.

George Minot Lectureship

The Section on Experimental Medicine and Therapeutics of the American Medical Association recently established the George Minot Lectureship in honor of Dr. Minot's contributions to medical knowledge of the causes and methods of control of pernicious anemia. The first lecture will be arranged during 1950 or 1951. Dr. Minot (Boston) has been a Fellow of the American College of Physicians since 1928.

Courses in Poliomyelitis

The University of Colorado Medical Center, aided by grants from the National Foundation for Infantile Paralysis, will give a series of postgraduate courses on Poliomyelitis, March 13–16, 1950, and May 22 to 27, 1950. The comprehensive care of patients in an epidemic will receive chief emphasis. Courses will be open to physicians west of the Mississippi River.

Dr. Thomas F. Walker, F.A.C.P., Great Falls, was recently installed as President of the Montana State Medical Association.

The Institute of Industrial Health of the University of Cincinnati conducted a course for physicians entitled "The Lead Problem in Industry," November 7 to 11, 1949. The course covered the background of the subject, of analytical and engineering considerations, inorganic lead intoxication, organic lead intoxication, economic and legal considerations. The class was limited to thirty-five physicians and the fee was $50.00.

Symposium on Inhalational Therapy

The Committee on Public Health Relations of the New York Academy of Medicine, in coöperation with the New York Association of Oxygen and Ambulance Services, will present a Symposium on Inhalational Therapy, consisting of exhibits, demonstrations, motion pictures, and lectures, at the Academy building, 2 E. 103rd Street, New York City, December 5 to 10, 1949. This course will bring to physicians interested in this field information about recent developments in this aspect of therapy and the efficient use of the equipment available for it.

Dr. J. Harry Murphy, M.D., F.A.C.P., was recently elected President of the Nebraska Tuberculosis Association.

A new periodical in an important field will begin publication in February 1950. It will be called "Angiology, The Journal of Peripheral Vascular Diseases." Editor-in-Chief will be Dr. Saul S. Samuels, Chief of the Department of Peripheral Arterial Diseases, Stuyvesant Polyclinic, New York City.

Among Associate Editors in the United States are Dr. Alton Ochsner, of Tulane; Dr. Keith Grimson, of Duke; Dr. Leo Loewe, of Long Island Medical College; Dr. D. W. Kramer, of Jefferson; Dr. Gerald Pratt, of N. Y. University Medical School. A number of prominent foreign physicians will also serve. The Williams & Wilkins Company, of Baltimore, will be the publishers.

Dr. Joseph B. Kirsner, F.A.C.P., of the University of Chicago, has been elected President of the American Gastroscopic Society.

"Circulation," New Official Journal of the American Heart Association

A new official monthly journal of the American Heart Association, "Circulation," will begin publication in January, 1950. The American Heart Association will terminate sponsorship of the monthly, "American Heart Journal," with the December, 1949 issue. This latter journal has been published heretofore for the Association by the C. V. Mosby Company.

Dr. Thomas M. McMillan, F.A.C.P., Philadelphia, continues as Editor-in-Chief for the Association.

The subscription rate will be $12.00 ($13.00 to foreign countries).

Enlarged Medical Center Planned at University of Michigan

According to the details of a plan announced by President Alexander G. Ruthven, the University of Michigan is planning an enlarged medical center within a few years. The cost is estimated at approximately twenty million dollars. Stimulus for the plan was based largely on the receipt of a grant of three million dollars from the Kresge Foundation of Detroit for the erection of a Medical Research Institute building, one of five new major units needed for the enlarged medical center. It is expected that the building will be started within a few months and will be erected just west of the University Hospital and attached to it. President Ruthven said that other buildings in the future plan will be an out-patient clinic, a maternity hospital, a medical and nursing education building, and a children's and infants' hospital.

The State Legislature at its last session appropriated $100,000.00 for the drawing of plans for an outpatient clinic which, along with the research building, had been regarded as foremost among unmet needs.

The University is fully cognizant of the necessity to provide medical education for a larger number of students. Present undergraduate enrollment of the Medical School is 494 students, 151 of them in the first year class. Nearly 1500 applicants must be rejected each year recently, some of them almost as well qualified as those who are accepted, but cannot be admitted for lack of facilities and teaching and clinical staff. This year only 10 applicants from outside Michigan were admitted.

United States Public Health Service Announces Regular Corps Examination for Medical Officers

A competitive examination for appointment of Medical Officers in the Regular Corps of the United States Public Health Service will be held on January 9, 10, and 11, 1950. Examinations will be held at a number of points throughout the United States, located as centrally as possible in relation to homes of candidates. Applications must be received no later than December 12, 1949.

The Regular Corps is a commissioned officer corps composed of members of various medical and scientific professions, appointed in appropriate professional categories such as medicine, dentistry, nursing, engineering, pharmacy, etc. All commissioned officers are appointed to the general service and are subject to change of station.

Appointments will be made in the grades of Assistant Surgeon (1st Lt.) and Senior Assistant Surgeon (Captain). Appointments are permanent and provide opportunities to qualified physicians for a life time career in clinical medicine, research, and public health.

Requirements for appointment in the grade of Assistant Surgeon: the applicant must be a citizen of the United States, at least 21 years of age, and a graduate from a recognized school of medicine. Physicians who are successful in the examination

and are now serving internships will not be placed on active duty in the Regular Corps until completion of internship. Applicants for appointment in the grade of Senior Assistant Surgeon must meet the above requirements and must have had a total of at least 10 years of educational training and professional experience subsequent to high school. The entrance examination will include written professional tests, an oral interview, and a physical examination.

The professional written examination for the grade of Assistant Surgeon will cover the following subjects: 1. anatomy, physiology, biochemistry; 2. materia medica and therapeutics; 3. obstetrics and gynecology; 4. practice of surgery; 5. practice of medicine; 6. epidemiology and hygiene; 7. pathology and bacteriology. Senior Assistant Surgeon applicants will be examined on subjects 4, 5, 6, and 7 listed above.

Gross pay is governed by the Career Compensation Act of 1949, and is identical to that of officers of equivalent rank in the Army and Navy. Under current law, entrance pay for an Assistant Surgeon with dependents is $5,686.56 per annum; for Senior Assistant Surgeon with dependents, $6,546. These figures include the $1,200 annual additional pay received by medical officers as well as subsistence and rental allowance.

Promotions. Provisions are made for promotion at regular intervals up to and including the grade of Senior Surgeon (Lt. Col.) and for selection for promotion to the grade of Medical Director (Col.).

Retirement pay after 30 years of service or at the age of 64, is three-fourths of annual base pay at the time of retirement. Retirement for disability is authorized under the Career Compensation Act and disability retirement pay is at a minimum, one-half of the annual base pay at the time of retirement.

Additional benefits include 30 days annual leave, sick leave, full medical care, and many of the usual privileges extended to members of the military forces.

Application forms and additional information may be obtained by writing to the Surgeon General, United States Public Health Service, Federal Security Agency, Washington 25, D. C. Attention: Division of Commissioned Officers. Applications received after December 12, 1949, will not be accepted for this examination, but will be admitted to the examination in May, 1950.

OBITUARIES

DR. WILLIAM RAMSEY BLUE

William Ramsey Blue, M.D., F.A.C.P., died in Memphis on September 8, 1949, following a long illness.

He was born in Gallatin, Tennessee, 61 years ago and received his medical degree from Vanderbilt University in 1911. He practiced with his brother, Dr. J. B. Blue, in Parkin, Arkansas, until he came to Memphis in 1918.

Being a very good student of medicine, he felt the need of postgraduate training. In 1917 he went to New York and worked at the Nursery and Child's Hospital, preparing himself for the specialty of pediatrics. This specialty he followed until sixteen years ago when he became interested in the field of internal medicine.

His ability to teach led to his appointment as Associate Professor of Medicine at the University of Tennessee College of Medicine.

In addition to being a life member of the American College of Physicians, he was a member of the Memphis and Shelby County Medical Society, the Tennessee State Medical Association and the American Medical Association.

Dr. Blue was in every way a credit to his profession. He hewed to the line on medical ethics and had no patience with anyone who was not willing to make every sacrifice to keep the practice of medicine on a very high plane.

WILLIAM C. CHANEY, M.D., F.A.C.P.,
Governor for Tennessee

WILLIAM WASHINGTON GRAVES

William Washington Graves, M.D., F.A.C.P., was one of the physicians who bridged over the changes in neuropsychiatry from the last two decades of the previous and the first half of the present century. Born in 1865 in LaGrange, Kentucky, and graduated with a Doctor of Medicine degree from the St. Louis College of Physicians and Surgeons in 1888, he early turned his special attention to the study of the basic sciences of anatomy, pathology and anatomic neurology, thus laying the ground work for his future specialization. He spent almost three years in Europe, particularly in Germany and Austria, as a roaming student, visiting all the great universities and registering for special courses under the great masters, the outstanding teachers of the first decade of the present century. When he returned to St. Louis in 1905, he became instructor in the Department of Neurology in the St. Louis University School of Medicine and continued as a faculty member of that institution up to the year 1948 when he became Emeritus Professor and Director Emeritus of his department. He was appointed to the professorship in 1914 and to the directorship of the department of Neurology and Psychiatry in 1925. He served as consultant in neurology in practically all of the hospitals of St. Louis at one time or another, both in the public as well as in the private institutions.

Dr. Graves's investigations, it is interesting to note, dealt with problems that were at first sight quite remote from the area of his clinical practice. The study of the structure and the characteristics of the shoulder blade might well at first sight seem to be a purely morphological study; for Dr. Graves, however, that study was the beginning of a long pathway into the unknown which he had projected and on which he progressed during more than thirty years, not very far, it must be admitted, but sufficiently far to have his efforts achieve significance. Dr. Graves became more and more interested in the relation between physical and mental characteristics and while it must be confessed that research in that field progressed faster than Dr. Graves himself could follow, nevertheless, his own personal philosophy won for him an invitation to discuss his viewpoints before the University of Edinburgh. If Dr. Graves's

morphological studies had been conducted a generation earlier, they would, no doubt, have contributed greatly to the progress of morphological and statistical genetics. As it was, they were conducted during the time when the study of heredity was leading into physiological and biochemical interpretations. Dr. Graves sensed this and with his accustomed insistent determination, he attempted to follow. Unfortunately, his health began to fail fully fifteen years ago, forcing him to place a limit on the incredibly long hours of devotion to the study which he had determined to make his life work. His mass of data and his osteological collection represent an expenditure of energy and time equalled to the knowledge of the writer by no other investigators, even by those who gave their full time to their research.

To know and understand Dr. Graves, one must understand and know not only his scientific and his clinical work but also his human characteristics, his kindliness, his broad sympathies, his desire to alleviate suffering—a desire which had been enormously stimulated by reason of his own personal sufferings, his idealism and, above all, his ability to interpret favorably to the individual almost any kind of transgression. He was one of those rare individuals who applied in his own life the full truth of the proverb, "To know all is to excuse all." By nature and by choice, innately as well as by his education and by his self-discipline, he was a gentleman. His long period of failing health and his sufferings were terminated by death on April 19, 1949.

ALPHONSE M. SCHWITALLA, S. J., Dean Emeritus,
St. Louis University School of Medicine.

DR. WILHELM S. ANDERSON

Dr. Wilhelm S. Anderson, F.A.C.P., Northfield, Minnesota, died June 26, 1949, at the age of 73, of coronary thrombosis. Dr. Anderson attended St. Olaf's College, then transferred to the University of Minnesota College of Medicine and Surgery from which he received his medical degree in 1903. He spent some periods of post-graduate study at Harvard Medical School and the New York Post-Graduate Medical School and Hospital. For a number of years he practiced medicine at Grand Forks, North Dakota. In 1927, he entered the U. S. Veterans Administration and served continuously in that service until his retirement about 1946. Dr. Anderson was a Diplomate of the American Board of Internal Medicine and had been a Fellow of the American College of Physicians since 1931.

DR. THOMAS KRAPFEL LEWIS

Thomas Krapfel Lewis, M.D., F.A.C.P., born in Merchantville, N. J., January 7, 1887, died in New Haven, Conn., August 28, 1949, of ventricular fibrillation, following an acute coronary occlusion five days previous.

His elementary education was received in the Merchantville public schools, following which he graduated from the New Jersey Friends' Academy of Moorestown, Haverford College in 1909, and the University of Pennsylvania School of Medicine in 1913. His internship was served at the Cooper Hospital, Camden, N. J., 1913–14.

As an internist he practiced in Camden, N. J., from 1914 until the time of his death, except for eighteen months while he served overseas in the First World War as Commanding Officer of the 165th Ambulance Company of the Rainbow Division.

Following his return from the army Dr. Lewis became active in civic, fraternal, and medical affairs. He was a Past President of the Camden Lions Club and a Past President of the Camden City and Camden County Medical Societies.

In 1921, he was appointed Attending Physician to the Cooper Hospital, and in 1946, he was elected Chief of the Medical Division of the Staff of this Hospital, which position he held until his death.

While Chairman of the Executive Committee of the Staff of the Cooper Hospital, he rendered a unique service by helping coördinate the interests of the Board of Managers and the Medical Staff.

Dr. Lewis was a prominent figure in the New Jersey Medical Society for many years, having served as a member of the Welfare Committee from 1933 to 1938, Chairman of the Sub-Committee on Medical Practice from 1933 to 1938, as Trustee in 1935. Some of his most valuable work was done while serving as Chairman of the Sub-Committee on Medical Practice of the State Society, in connection with the distribution of medical care. During this period he attracted wide attention by his analysis of the problem of the medical care of the indigent. Keenly interested in the Voluntary Plan movement, Dr. Lewis was a member of the various committees appointed by the State Medical Society to study the organization of a medical service plan, and he was actively associated with both the Medical Service Administration and the Medical Surgical Plan since their inception in 1938, serving as president of each organization since 1942.

Dr. Lewis served with distinction from 1942 until the time of his death as a member of the House of Delegates of the American Medical Association from New Jersey.

He was elected a Fellow of the American College of Physicians in 1939. His city and state have lost a good citizen and an outstanding physician. Those associated with him at the Cooper Hospital and in the New Jersey State Medical Society will long remember him as an untiring worker in the interests of organized medicine and the public welfare.

RALPH K. HOLLINSHED, F.A.C.P.

DR. G. CARROLL LOCKARD

On August 7, 1949, Dr. G. Carroll Lockard, F.A.C.P., of Baltimore, died as a result of complications following an operation.

Dr. Lockard was born in Baltimore in 1882. He attended Baltimore City College and University of Maryland, graduating in 1903.

At the time of his death, Dr. Lockard was Professor of Clinical Medicine at the University of Maryland School of Medicine and Visiting Physician at the University Hospital. He was a Diplomate of the American Board of Internal Medicine, a member of the Medical and Chirurgical Faculty of the State of Maryland, of the American Medical Association, and a Fellow of the American College of Physicians, attaining this honor in 1923.

Dr. Lockard was one of Baltimore's leading physicians, and was best known in the teaching life at the University of Maryland School of Medicine. He was honored and loved by all his students, and in his passing Baltimore has lost a very fine physician and, to those who knew him, a good friend.

WETHERBEE FORT, M.D., F.A.C.P.,
Governor for Maryland

DR. CECIL McKEE JACK

Dr. Cecil M. Jack died June 28, 1949. He was born in Decatur, Ill., November 15, 1876. He received his Ph.B. in 1899 and his M.D. in 1902 from the University of Michigan. For a great many years he was connected with the Decatur and Macon County Hospital and the Decatur Contagious Hospital. He served as President of the Macon County Tuberculosis Board, Macon County Tuberculosis Sanatorium. He was a Diplomate of the American Board of Internal Medicine, a member of the National Tuberculosis Association, Illinois State Medical Society, Illinois Trudeau

Association, a former president of the Decatur Medical Society and the Illinois State Tuberculosis Association. He had been a Fellow of the American College of Physicians since 1919 and served as Governor of the College for Southern Illinois since 1941.

A number of years ago, Dr. Jack initiated legal action and won the principle that the expenses for professional travel to scientific meetings shall be deductible from income in connection with the Federal Income Tax. This has saved physicians and allied professional men literally hundreds of thousands of dollars annually.

A smiling face and a warm handshake greeted his friends and colleagues at each and every meeting of the College, regional and national. He gave his time and effort in building the American College of Physicians and aided in selecting physicians who would be a credit to our College.

Dr. Jack was an outstanding internist in his community and his opinions were built on honesty and keen clinical judgment. We shall miss him as our true friend and Governor in Southern Illinois.

GEORGE W. PARKER, M.D., F.A.C.P.

DR. PAUL EDWARD SIMONDS

Dr. Paul Edward Simonds, F.A.C.P., Riverside, Calif., died July 10, 1949, age 72. He was born in Detroit, Mich., October 12, 1876, pursued two years of collegiate work at Napa College and the University of Denver. He received his medical degree from the University of Southern California School of Medicine in 1908. He was a past Secretary, past Vice President and past President of the Riverside County Medical Association, past President of the Southern California Medical Association, a member of the California State Medical Association and of the American Medical Association. He had been a Fellow of the American College of Physicians since 1930, and he was a Diplomate of the American Board of Internal Medicine. His special interests were in the field of Internal Medicine and Geriatrics. In his later years, his practice was very limited. For more than twenty-five years, he had made a great contribution to the Boy Scout movement in the Riverside area. He was a family physician in the finest sense and contributed a great deal in keeping the practice of medicine in his county at a high level.

DR. ROBERT EDWARD WESTMORELAND, SR.

Dr. Robert Edward Westmoreland, Sr., an Associate of The American College of Physicians since 1947, aged 40, Chief of the Medical Service at the Veterans Administration Hospital in Indianapolis, died June 30, 1949, at the Mayo Clinic in Rochester, Minnesota, of cardiac failure.

Dr. Westmoreland was born at Petersburg, Virginia, July 17, 1908. He received his B.S. from the University of Virginia in 1928 and his M.D. from the University of Virginia Department of Medicine in 1932. He interned from 1932 to 1934 at the New York Postgraduate Hospital, and thereafter was Assistant Physician to the Hospital and Attending Physician to the Dispensary for some years. He served in the Medical Corps, U. S. Army from 1942 to 1946, attaining the rank of Major. Thereafter, he entered the Veterans Administration and became Chief of the Medical Service at the Indianapolis Veterans Administration Hospital. He was a member of the New York County Medical Society, the State of New York Medical Society and the American Medical Association, and a diplomate of the American Board of Internal Medicine.

DR. JACOB JOHN WESTRA

Dr. Jacob John Westra was born March 2, 1908, in Grand Rapids, Michigan, and died in Champaign, Illinois, July 17, 1949.

Dr. Westra received his B.A. degree from Calvin College of Grand Rapids, Michigan, in 1929, and his Ph.D. degree in physiology from the University of Chicago in 1933. He then taught physiology at the University of Texas Medical School for two years, following which he returned to Chicago and entered Rush Medical College as a student where he received his M.D. degree in 1937. He served a two-year internship at the Presbyterian Hospital in Chicago from 1936 to 1938. He then entered the Mayo Clinic as a Fellow in Internal Medicine, continuing to October, 1939. From 1940–44 he was in private practice. In 1944, he joined the Staff of the Christie Clinic of Champaign, Illinois. He was on the Attending Staffs of the Burnham City Hospital and the Mercy Hospital, and served as Civilian Consultant in Internal Medicine at the Chanute Air Base in Rantoul, Illinois.

Dr. Westra was an Associate of the American College of Physicians (1945), a Diplomate of the American Board of Internal Medicine, and a member of Sigma Xi and Alpha Omega Alpha. In 1948 and 1949, he was Secretary of the Champaign County Medical Society, and during this time he was very active before the public of his community as an opponent of the proposed compulsory national health insurance legislation. His loss to the community is greatly felt. He was a respected clinician, teacher and leader.

CHARLES H. DRENCKHAHN, M.D., F.A.C.P.,
Governor for Southern Illinois

THE AMERICAN COLLEGE OF PHYSICIANS

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31ST ANNUAL SESSION
AMERICAN COLLEGE OF PHYSICIANS

MECHANICS BUILDING

BOSTON, MASS., APRIL 17–21, 1950

President (General Sessions and Morning Lectures), Reginald Fitz, M.D., Boston, Mass.

General Chairman (Clinics and Panels), Chester S. Keefer, M.D., Boston, Mass.

The staffs of the many distinguished medical schools and hospitals of the Boston area will provide an exceptionally fine program of lectures, panel discussions and hospital clinics. A large attendance is anticipated. Full details concerning hotel accommodations, etc., and the tentative program of the Session will be presented in College News Notes in the ANNALS OF INTERNAL MEDICINE during the coming months.

1949 DIRECTORY
THE AMERICAN COLLEGE OF PHYSICIANS

Editing of a completely new and revised Directory of the College was concluded October 1, 1949. Printing and binding to be completed during November.

Orders already filed will be filled at once and billed.

Edition is limited.

Post-publication Price, $5.00.

E. R. Loveland, *Exec. Sec.*
4200 Pine Street
Philadelphia 4, Pa.

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MANUSCRIPTS. All correspondence relating to the publication of papers and all books and monographs for review should be addressed to the Editor. No manuscripts will be accepted without his consideration. Bibliographic references are to conform to the following style:

4. Doe, J. E.: What I know about it, J. A. M. A. 96: 2006, 1931.

Six illustrations per article are allowed without cost to the author. Beyond this number the author must pay the actual cost of illustrations.

REPRINTS. For each article published, there will be furnished gratis fifty reprints without covers. An order slip for additional reprints, with a table showing cost, will be sent with galley proof to each contributor. If additional reprints over the first fifty are wanted the order slip must be returned to the printer at the time corrected galley proofs are sent to the Editor.

REVIEWS. The ANNALS will make an especial feature of the reviews of monographs and books bearing upon the field of internal medicine. Authors and publishers wishing to submit such material should send it to the Editor. While obviously impossible to make extended reviews of all material, an acknowledgment of all books and monographs sent will be made in the department of reviews.

SUBSCRIPTION. This periodical is issued monthly, new volumes beginning with the January and July numbers of each year. Subscriptions may be by volume or by year. Volumes will consist of approximately 1,300 pages. Subscription price per annum, net postpaid: $10.00, United States, Canada, Mexico, Cuba, Hawaii, Puerto Rico, Philippine Islands, Central and South American Countries, and Spain; $11.00, other countries. Prices for back volumes or numbers furnished upon application. Single numbers, current volume, when available, $1.25. Members of the American College of Physicians receive the ANNALS OF INTERNAL MEDICINE in connection with the payment of annual membership dues, of which nine dollars is for a year's subscription to the publication. Checks should be drawn to the order of W. D. STROUD, M.D., Treasurer, and remitted through the Publication Office or the Executive Secretary's Office.

BUSINESS CORRESPONDENCE. All correspondence relating to business matters, advertising, subscriptions to the ANNALS, inquiries concerning membership in the American College of Physicians, et cetera, should be addressed to the Publication Office or to the Executive Secretary. Books and reprints presented to the College Library should be addressed to the Executive Secretary.

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